ECONOMIC EVALUATIONS OF VACCINES IN CANADA: EXPLORING THE EPIDEMIOLOGIC AND ECONOMIC IMPACT OF CHICKENPOX VACCINE STRATEGIES IN CANADA USING AN AGENT-BASED MODEL

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By

Ellen Ruth Stalker Rafferty

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ABSTRACT

Health economic evaluations are a systematic method of measuring and valuing the costs and effects of different health interventions. The cost-effectiveness of vaccines is particularly difficult to measure, as they are generally complicated by the infectious nature of the diseases. Using a scoping review framework, we gathered, summarised and described the evolution of published economic evaluations of vaccines in Canada. In recent years there has been a consistent increase in vaccine cost-effectiveness studies in Canada, with more studies adhering to Canadian economic evaluation guidelines. However, the two Canadian cost-effectiveness studies looking at universal chickenpox vaccination were conducted prior to the implementation of the program in Canada, and with limited knowledge of the actual cost or effectiveness of the vaccine.

We built an agent-based model (ABM) to aid in the understanding of chickenpox and shingles disease dynamics, to measure the cost-effectiveness of chickenpox vaccination and to help guide health policy decision-making. Chickenpox is a childhood disease caused by varicella-zoster virus (VZV), which can reactivate as shingles in adulthood. While natural waning of VZV cell-mediated immunity (CMI) can lead to shingles reactivation, one theory posits contact with a shingles or chickenpox case may boost an individual's VZV-CMI (i.e. exogenous boosting), offering protection from shingles. Using the ABM, we tested several quantitative theories of VZV boosting, as well as the impact of chickenpox vaccination on shingles epidemiology. Our model highlighted the importance of not only knowing when, and if, the VZV exogenous boosting events occur but the duration an individual remains immune following a boosting event.

In Canada, there are eight different schedules, including diverse types of vaccines, ages of administration, number of doses for the chickenpox vaccine. Using the ABM we were able to test the effectiveness and cost-effectiveness of two main chickenpox vaccine schedules (schedule 1- MMRV at 12 months and 4-6 years; schedule 2- MMRV at 12 months and 18 months). We found differences in effectiveness and costs between the two schedules were relatively minor, suggesting other considerations, such as the current vaccine strategy and public preference may play a bigger role in determining the most appropriate chickenpox vaccination schedule.

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LIST OF ABBREVIATIONS

ABM	Agent-based model
AIDS	Acquired immunodeficiency syndrome
CADTH	Canadian Agency for Drugs and Technologies in Health
CMI	Cell-mediated immunity
DNA	Deoxyribonucleic acid
DoB	Duration of boosting
HIV	Human immunodeficiency virus
HPV	Hum papillomavirus
IgG	Immunoglobulin G
IHDA	Interactive Health Data Application
MMR	Measles, mumps, rubella
MMRV	Measles, mumps, rubella, varicella
NHS	National Health Service
PCR	Polymerase chain reaction
PCV	Pneumococcal vaccine
QALY	Quality adjusted life years
QoL	Quality of life
LDI	Long dosing interval
SDI	Short dosing interval

US	United States
VZV	Varicella Zoster Virus
WoI	Waning of immunity coefficient
WHO	World Health Organization

CHAPTER 1- INTRODUCTION

Chickenpox is generally a self-limiting childhood disease caused by varicella-zoster virus (VZV). Following primary infection VZV can remain latent in the sensory ganglia for future reactivation as shingles. Reactivation of VZV is generally associated with a decrease of VZV cell-mediated immunity (CMI) (i.e. waning of natural immunity) due to aging and senescence. In parallel to the natural waning of VZV-CMI immunity, one theory posits boosting of immunity occurs on contact with a chickenpox or shingles infected individual (exogenous boosting) and this process may limit shingles reactivation. One area of interest is the association between chickenpox vaccine and shingles disease, especially as previous models have predicted a sharp increase in shingles incidence rates following the implementation of universal chickenpox vaccination and therefore the reduction of natural VZV boosting. Flexible and complex models like agent-based models (ABM) offer a platform to test research questions related to chickenpox vaccination and shingles, including measuring the impact of a variety of plausible assumptions about the waning and boosting of VZV immunity on disease outcomes. An ABM can also help examine policy-relevant research questions, including the most appropriate timing and scheduling for the two chickenpox vaccine doses currently offered as part of the routine vaccination schedule in Canada. Furthermore, as health sector budgets become increasingly strained it is also important for policy-makers to consider how to implement effective public health programs while keeping costs at a minimum. ABMs can be used to estimate the cost-effectiveness of the chickenpox vaccine and of various vaccination schedules.

1.1. Rationale and aims of this research

1.1.1. Economic evaluations of vaccines

At the most basic level, economic evaluations try to identify, measure and value the costs and consequences (inputs/outputs) of different interventions [1]. By measuring the associated costs and benefits, economic evaluations of vaccines aim to test whether a vaccination program is worth doing compared to another intervention (e.g. treatment), as well as compare the cost-effectiveness of various implementation methods for the vaccination program [2]. However, testing whether a health intervention is worth doing compare with another health intervention can be difficult, and is based on a variety of factors, including cost, effects (e.g. life-years, quality adjusted life years) and/or willingness-to-pay. Often the widespread use, reimbursement

and overall recommendations for a vaccine are contingent on transparent and favourable cost-effectiveness [3]. Therefore, most developed countries have committees or organizations that measure the cost-effectiveness of each new vaccine to inform vaccine decision-making [3].

Economic evaluation of vaccines are often complicated by the fact that vaccination aim to prevent the spread of infectious diseases, and, as such, can have unintended population effects external to the individual-level protection afforded by the vaccine (i.e. externalities) [3,4]. Examples of possible externalities, or unintended consequences, of vaccination include herd immunity, shifting age of infection or strain replacement [3,4]. Therefore, economists must consider how both negative and positive externalities may impact the cost-effectiveness of a vaccine [3,4]. One method to measure the impact of externalities on disease outcomes is infectious disease modelling. Economic evaluations, specifically those focused on vaccination, are increasingly using modelling to estimate the costs and benefits of various health interventions [5]. As described by Kim et al. [6, p.434] "models are a simplified description of the underlying processes leading to disease and resource utilization and provide a formal framework to synthesize information from various sources". In general, using infectious disease modelling to measure the cost-effectiveness of a vaccine is important, as it can: (i) predict the duration of immunity based on immune correlates of protection, (ii) discount costs and benefits, (iii) evaluate alternative vaccination strategies not tested in clinical trials, (iv) evaluate the long-term benefits of the intervention and (v) estimate the indirect consequences of vaccination [3]. The model needs to be dynamic to account for externalities; that is, the model must take into consideration the force of infection changing over time [3]. To aid in the development of relevant and accurate cost-effectiveness results, specific guidelines are available for the production of economic evaluations of vaccines and the models used to conduct these analyses [2,6].

Model type (e.g. compartmental versus individual, dynamic versus static) is one of many decisions that needs to be made when conducting economic evaluation of vaccines; other decisions include the target population, study question, type of evaluation, comparator, perspective, and time horizon [2,4]. Consequently, there is the potential for a wide diversity in study design and quality of economic evaluations of vaccines being produced worldwide and in Canada. As a result of the foregoing, it is important to systematically gather, review and summarise Canadian economic evaluations on vaccines, with the goal of describing general

trends and gaps in the literature. Furthermore, a review of the literature can help identify novel and interesting research questions that address the identified gaps in the literature.

1.1.2. Chickenpox and shingles

Chickenpox is a childhood disease caused by VZV, which can reactivate as shingles following initial infection. In Canada, prior to chickenpox vaccination in 2001, chickenpox was very prevalent, with approximately 350,000 chickenpox cases per year, and 90% of children having the infection before age 12 [7]. Shingles is generally a more serious disease than chickenpox, causing significant radicular pain that lasts for a prolonged period, and a multitude of complications, including post-herpetic neuralgia (prolonged neurogenic pain), sight-threatening eye infections and secondary bacterial infections [8].

Reactivation of latent VZV in the form of shingles is generally associated with a waning of VZV cell-mediated immunity (CMI) over time. In parallel to the natural waning of VZV-CMI immunity, one theory posits that exogenous boosting of VZV-CMI decreases an individual's likelihood of shingles reactivation [9–11]. Exogenous boosting occurs when a VZV-immune individual is exposed to a case of chickenpox or shingles, leading previous models to predict a sharp increase in shingles rates following chickenpox vaccination. There remain several unknowns surrounding the epidemiology and economics of chickenpox disease and vaccination, and its impact on shingles infection.

1.1.3. Agent-based modelling of chickenpox and shingles

Previous models, along with epidemiological and immunological studies, have demonstrated that contact with the VZV (i.e. contact with a chickenpox or shingles case) may boosts one's immunity to VZV, and therefore reduce their risk of getting shingles in the future [9–11]. These same studies frequently show that chickenpox vaccination can reduce this boosting in the population, and therefore lead to an overall increase in shingles incidence; however, the empirical data to-date is largely inconclusive [12–16]. Adding to the confusion is the fact the quantitative values for the duration of immunity following exogenous boosting and the waning of natural VZV immunity remain largely unknown [16–18]. These concerns have raised questions about the impact and effectiveness of chickenpox vaccination and have left many countries debating whether to include the chickenpox vaccine in their routine immunization schedules [19]. One method of expanding our understanding of the dynamics

between chickenpox and shingles is to use infectious disease modelling, specifically agent-based modelling.

1.1.4. Optimal scheduling of the chickenpox vaccine in Canada

In Canada, many policy-makers are grappling with optimal universal vaccination schedules (e.g. number and timing of vaccine doses) for a variety of vaccinations (e.g. chickenpox, pertussis, HPV) to ensure high coverage rates and effective prevention of disease in the populations most at risk. For instance, there is a continued debate in Canada about the most effective pertussis vaccination schedule, including how many doses to give and when to give them, along with questions about whether vaccination program should focus on pregnant mothers, or cocooning around young infants [20,21]. There is also a debate in Canada around the timing of the chickenpox vaccine. All provinces and territories have some form of universal chickenpox vaccine, but there were eight different ways of delivering the vaccine (i.e. number of doses, dose timing, vaccine combinations) across the country in 2017 [22]. Agent-based modelling could provide some insight into the effectiveness of different chickenpox vaccine schedule, allowing the testing of a variety of vaccine schedules without having to consider the confounding factors that could influence disease outcomes in real-world data analysis.

1.1.5. Economic evaluation of chickenpox vaccine in Canada

While studies have measured the cost-effectiveness of chickenpox vaccination overall, to our knowledge none have tested the cost-effectiveness of the different vaccine schedules, particularly as each vaccination strategy may lead to diverse costs and effects, such as different ages of infection, incidence of shingles and chickenpox, vaccine uptake and number of vaccination doses. Moreover, currently in Canada there are a lack of post-implementation economic evaluations, including analyses on the chickenpox vaccination. Post-implementation economic evaluations are vital, as cost and outcome data is often lacking prior to the introduction of the vaccine, and the ability to predict the vaccination impact, particularly herd effects, is limited [23]. For instance, prior to vaccine implementation, it is often difficult to predict the ultimate market price of a vaccine, which can vary dramatically in space and time. While sensitivity conducted in the original cost-effectiveness studies may explore these unknown values, this will create more uncertainty around the final cost estimates, as was evidenced in Brisson et al. [24] where the results were very sensitive to vaccine price. Therefore, there is a need to evaluate whether existing vaccination programs are good value for their cost [23]. These

post-implementation studies allow researchers to validate estimates of costs and outcomes from pre-implementation evaluations, and judge the ability of pre-implementation analyses to predict the cost-effectiveness of the vaccine, potentially improving future studies [23]. This type of economic evaluation may be particularly important for chickenpox, as the original cost-effectiveness studies demonstrated that chickenpox vaccination was only cost-effective under certain circumstances, and the outcomes of the analysis were sensitive to a variety of unknown factors, such as the price of the vaccine, vaccine efficacy and vaccine strategy [24–26].

1.2. Theoretical foundation for the research

1.2.1. History and economic theories underlying economic evaluations

The scarcity of resources in health care require the development of methods to frequently and systematically evaluate health care alternatives [27]. Health economists suggest that these decisions should be based on economic efficiency; where societal net benefits are maximized. Economic evaluation methods to measure the value of different health alternatives have developed over time to guide decisions and policymaking [27].

Supply and demand theory developed by Adam Smith emphasized that choices reflect both values and preferences, along with scarcity, and suggested that individuals weigh the marginal benefits (i.e. utility) and costs of different options before making a decision [28]. Building on Adam Smith's work, economists theorized that the concepts of supply and demand would result in the maximum benefit for the minimum price, or the efficient allocation of resources [28]. Neo-classical economists found a way to formalize Adam Smith's insights, through the theory of general equilibrium, which argues that individuals choose a bundle of goods from the market to maximize their utility, where the bundled options are restrained by their budget [28]. In comparison, 'firms' choose their inputs and outputs to maximize profits, which is restrained by their capacity for productivity [28]. These two competing forces ensure that in the perfect market, prices will adjust until supply equals demand and equilibrium is reached [28]. In this case, the price of the good is consistent with the market's valuation of it.

However, the goals and aims of society may differ substantially from individual preferences, and studies based on individuals may not consider societal issues [28]. Therefore, to deal with the issue of how to allocate societal resources, welfare economic approaches were developed. "Welfare economics is concerned with social welfare", and therefore the costs and benefits of goods and services for society as a whole [2, p.9]. One of the first approaches was to

use the competition model described above to determine optimal social welfare. This method assumes that individuals can judge their own welfare, they are rational, the intervention can benefit one person without disadvantaging another, and there are no externalities (i.e. individuals' utility functions do not overlap). Therefore, the optimal position (Pareto efficiency) in this framework is when it is no longer possible to improve an individual's welfare without impairing another individual's welfare; specifically, societal welfare is increased if everyone gains from a policy. Kaldor and Hicks built on the Pareto criterion to address the issue that policies often have both winners and losers [28,29]. They developed a variant of the Pareto criterion, called the Kaldor-Hicks criterion, which included assumptions about an individual's willingness-to-pay for a benefit or willingness to accept money for a loss [28,29]. The Kaldor-Hicks criterion, that suggests a "project is undertaken if the net social benefits (defined as social benefits minus social costs) are positive." [2, p.20], therefore those who are better off from an intervention could, in theory, compensate those who are worse off or re-allocate resources.

The valuation of health care programs and/or goods is particularly difficult, mainly because health care goods and the market for these goods are very different from other kinds of goods/markets [27,28]. First, individuals are not always rational with regards to health care (i.e. do not always make decisions that are best for their health) and individuals may find it difficult to judge their own welfare. Second, it may be difficult for an individual to reveal their health preferences or know their health preference *a priori*. Third, there is significant uncertainty concerning one's future health and the outcome of the health intervention, making valuing the health needs (i.e. services or goods) of individuals difficult. Finally, there is significant asymmetry of information in health care. For instance, doctors often have more knowledge of certain aspects of an individual's health (e.g. treatment and pharmaceutical options) than they do [27,28].

The imperfections in the health care market may lead to issues in the valuation of the benefits of health care interventions, and therefore make it difficult to determine the appropriate allocation of resources. Furthermore, because of the widespread use of health insurance, prices do not commonly appear at point of consumption in the health care market, and consequently economists developed other methods for valuing health care interventions and/or services, including: (1) the welfarist approach, which aggregates individual values across society (e.g. aggregating willingness-to-pay for certain benefits) or (2) social decision-maker approach, where

the decision maker for society determines the appropriate valuation for a benefit [28]. These different methods for evaluating health care interventions aim to measure efficiency, including: (1) technical efficiency, which is concerned with the maximum improvement in an outcome for a specific amount of resources (i.e. what is the best outcome we can achieve with these resources?); (2) productive efficiency, which is the minimization of costs for a given benefit or the maximization of health benefit for a specific costs (i.e. which different combination of resources will achieve the best outcome); and (3) allocative efficiency, that considers how benefits are allocated among persons in a society, in combination with how resources are used to produce health (i.e. what is the right group of health care programs for our budget?) [28]. Allocative efficiency is particularly important as many health intervention lead to both an increase in costs as well as an increase in effects, and therefore decisions need to be made about which patient groups get the extra resources and benefits.

To measure these different types of efficiency and allocate scarce resources, economists developed economic evaluation, which evaluates interventions for their costs and benefits simultaneously [28]. Economic evaluations are a part of the health technology assessment process, where a health intervention or technology is systematically evaluated based on its social, economic, and ethical impact. In economic evaluation costs at the margin are considered (i.e. the cost of producing one extra unit of benefit); including incremental direct and indirect costs (e.g. opportunity costs) associated with implementation of the intervention. Simultaneously the benefits of the health intervention are evaluated; with the specific aim to identify the value of the health outcome associated with the intervention [28]. The method for measuring benefits determines the type of economic evaluation produced, with three main types in existence today, cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA) [27,28].

CEA generally uses natural units that measure one-dimensional effects of the health outcome (e.g. deaths, cases). Therefore, CEA generally evaluates productive efficiency. However, there are many situations where health outcomes cannot be described by one element of the disease, in these cases a more general measure of value is used [27,28]. These types of economic evaluations, CUAs, use utility measures, such as Quality Adjusted Life-Year or Disability Adjusted Life Years to measure benefits both in terms of quantity (e.g. life-years) and quality [27,28]. Although, CUA is a broader measure of benefit and value, it is still primarily

concerned with productive efficiency. The broadest measure of value, and the one economists argue best captures social welfare is CBA. This method employs a monetary measure of utility, which is typically measured by asking individuals their willingness-to-pay for certain interventions or improvements in their health status [27,28]. Therefore, CBA, in comparison to CEA and CUA, can also answer whether the goal of the intervention is worth pursuing at all, and as such, it is a measure of allocative efficiency. However, many economists have raised concerns with the measurement and methodological limitations associated with measuring individuals' willingness-to-pay for health interventions [30–32]. For instance, willingness-to-pay estimates are often under-sensitive to the magnitude of the benefit, therefore individuals completing contingency valuation surveys often give similar answers for a wide range of reductions in death or injury, and as such, overestimate the value of small risk reductions [33]. Furthermore, willingness-to-pay surveys often over-estimates the impact of the intervention, as respondents will pay more for an intervention when asked about it in isolation, in comparison to when they are asked about it in conjunction with other interventions [33].

While these three types of economic evaluation continue to be used to improve the technical, productive, and at times, the allocative efficiency of the health care system, debates continue in the literature about how best to measure benefits, what benefits to include when conducting an economic evaluation of health care, and which method best captures social welfare [27,28].

1.2.2. Theoretical foundation and history for agent-based modelling in economic evaluations

Economic evaluations are one form of health technology assessment (HTA), a type of analysis used to make decisions regarding health interventions and programs [34]. Economic evaluations are often done alongside clinical trials to evaluate the costs associated with a health intervention, as well as the effectiveness. Clinical trials offer a convenient method for measuring the cost-effectiveness of an intervention early in the decision-making process. However, there are many limitations to this approach, including the inability to account for costs and outcomes over extended periods of time, the incapacity for evaluating programs that did not undergo clinical trials, and the inability to capture realistic costs associated with a health program [34]. For example, economic evaluations based on clinical trials need to account for the higher level of health care patients often receive (e.g. greater number of tests, greater degree of health care contact) and cannot measure costs or effects over long time horizon. Therefore, economic

evaluations, alongside other forms of health technology assessment started using decision-analytic models. These models "represent an explicit approach to synthesising currently available evidence regarding the effectiveness and cost of alternative (mutually exclusive) healthcare strategies" [7, p.356]. These types of analysis have exploded in recent years, especially as health interventions become increasing complex, with implications stretching into the future. One type of decision-analytic model that has become increasingly popular in recent years are ABMs.

ABMs are dynamic models with a focus on individuals (i.e. agents), each of whom have their own characteristics and behaviour based on a set of rules prescribed in the model [35]. These agents interact with each other and their environment, and their behaviour, actions and characteristics can change over time [35]. Thus, the defining element of ABMs is their 'bottom-up' approach to representing a dynamic process or system (e.g. infectious disease), allowing the collection and interaction of agents in an environment to determine the population level outcomes [35]. These elements allow for complexity and flexibility in model design, with the opportunity to alter a variety of different parameters at both the individual (e.g. age, sex, location, attitude, disease state) and the population (e.g. public health alerts) levels. These elements differentiate ABMs from other types of models, including system dynamic and discrete event simulation models. **Chapter 3** and **4** discusses in more detail the benefits and limitations associated with agent-based modelling.

1.3. Outline of thesis

The organization of this thesis is as follows:

Chapter 1 introduces the thesis and outlines and summarizes the goals of the research for the subsequent chapters.

Chapter 2 (Article 1) systematically gathers, reviews and summarises Canadian economic evaluations on vaccines using a scoping review methodology, with the goal of describing general trends and gaps in the literature. This chapter also helped identify novel and interesting research questions for this thesis.

Chapter 3 provides a general overview of the history and epidemiology of chickenpox and shingles diseases, and the chickenpox vaccine, worldwide and in Canada to provide context for Chapters 4, 5 and 6. In this chapter, five fundamental aspects of chickenpox and shingles diseases are discussed: (1) VZV and immunology, (2) chickenpox disease and epidemiology, (3)

shingles disease and epidemiology, (4) chickenpox and shingles vaccination, and (5) infectious disease modelling.

Chapter 4 (Article 2) presents details on the building and calibration of an agent-based chickenpox and shingles model, in order to simulate the epidemiology, transmission and outcomes of these two diseases. Using this model, we test how chickenpox vaccination impacts the incidence and age-distribution of shingles over 75 years post-vaccination, taking into consideration a variety of plausible assumptions about the waning and boosting of VZV immunity. It also present details on the building of the ABM that was used to conduct the analyses in Chapters 4, 5 and 6.

Chapter 5 (Article 3) determines the effectiveness of the chickenpox vaccine over time and the optimal vaccine schedule by comparing the disease outcomes under several universal vaccination strategies currently employed in Canada, using the ABM constructed in Chapter 4. Furthermore, this chapter summarizes updates to the ABM needed to test the effectiveness of two chickenpox vaccination schedules.

Chapter 6 (Article 4) measures the overall cost-effectiveness of chickenpox vaccine post-implementation both considering and ignoring the impact on shingles incidence. In this chapter we also analyse the costs and benefits of two different chickenpox vaccination schedules, to measure whether the timing of vaccine delivery has an impact on its cost-effectiveness. Furthermore, this chapter outlines updates to the ABM that were necessary to measure the costs and benefits of chickenpox vaccination and disease outcomes.

Chapter 7 concludes the thesis by summarizing the key findings, outlining limitations of the research and suggesting areas for future exploration.

This thesis did not require ethics approval as it used no individual data, and only included estimates from the literature in the building of the ABM and the running of experiments. However, we received ethical approval for the building of a chickenpox and shingles ABM, in conjunction with other projects related to infectious disease modelling of childhood infections. A copy of the notification of approval is available in **Appendix A**.

1.4. References

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CHAPTER 2- ECONOMIC EVALUATIONS OF VACCINES IN CANADA: A SCOPING REVIEW

Article reproduced with minor edits. Originally published as: Rafferty ERS, Gagnon HL, Farag M, Waldner CL. Economic evaluations of vaccines in Canada: a scoping review. *Cost Eff Resour Alloc 2017*;15(7):1-12. My contributions to this manuscript included conceiving and designing the review, reviewing articles for inclusion/exclusion, conducting analysis and interpretation of the data, and preparing the manuscript. Heather Gagnon reviewed potential articles for inclusion/exclusion and helped critically revise and finalize the document. Dr. Marwa Farag and Dr. Cheryl Waldner aided in conception and design of the study, the interpretation of findings, and helped critically revise and finalize the document.

As the number of economic evaluations of vaccines continue to grow it is important we assess the current state of this expanding and meaningful literature. Therefore, in this chapter we aim to summarise and describe the evolution of published economic evaluations of vaccines in Canada. Using Arksey and O'Malley's scoping review framework we assembled relevant research from both academic and grey literature. In this chapter we study the economic evaluation of vaccines literature for trends, strengths/weaknesses, transparency in reporting and gaps in research questions. We use the findings from this chapter to inform the focus the rest of the thesis.

2.1. Introduction

Vaccination is lauded as one of public health's most significant achievements, contributing to improvements in morbidity, mortality and quality of life worldwide [1,2]. Originally, one of the major advantages of vaccination as a public health intervention was their low cost, as many of the classic Expanded Program on Immunization vaccines only cost a few cents per dose and were cost-saving to the healthcare system [1,3]. However, in recent years more technologically complicated vaccines (e.g. subunit, gene-based vectors, particle-based) and more strict licensing regulations for vaccine safety and efficacy testing have led to more expensive vaccine development and manufacturing, which raise the question of vaccine cost-effectiveness [3].

With ongoing debates in many countries concerning the implementation and funding of these new vaccines, especially within the context of growing financial strain on healthcare systems, economic evaluations are becoming increasingly important to policy-makers [3]. Economic evaluations can improve the quality and consistency of decision making by providing a systematic way of comparing whether a specific vaccination program should be adopted compared with doing nothing or implementing an alternative intervention (e.g. treatment, other vaccines). Economic evaluations can also help evaluate scheduling and target population(s) [4,5].

The number of vaccine-related economic evaluations has substantially increased in the last few years. However, we have very little knowledge of the coverage and quality of this research, as well as the potential gaps and limitations of these studies. [6]. Systematic reviews on economic evaluations of immunizations generally focus on the results from a particular vaccine; recent examples include varicella [7] and influenza [8]. Meanwhile, many countries have yet to review and synthesize their own research in this area. One of the few examples is Spain, who recently released two comprehensive systematic reviews on Spanish economic evaluations of vaccinations completed between 1990-2012 [9,10].

In comparison, researchers in Canada have never fully synthesized the extent and characteristics of research on economic evaluations of vaccines in Canada. As the number of licensed vaccines in Canada and the number of economic evaluations on those vaccines continue to increase, it is essential that Canada begins to critically analyse and summarise this work [6,11]. This research is important to ensure improvement in the usefulness, quality and applicability of vaccine-related economic evaluations and the decisions they inform.

Furthermore, as countries produce similar evidence, comparisons of reporting, methods and results between countries could contribute to the international discussion on the major gaps in the literature and the quality, standardization and transparency of these studies.

This study aims to systematically gather, review and summarise Canadian economic evaluations on vaccines using a scoping review methodology, with the goal of describing general trends and gaps in the literature.

2.2. Methods

2.2.1. Scoping review methodology

We based our methodology on Arksey and O'Malley's (2005) [12] five step framework for conducting a scoping review, including (1) forming the research question, (2) identifying relevant studies, (3) study selection, (4) charting the data and (5) summarising and reporting the results. Each section is described in more detail below. Scoping reviews are designed to summarise rich and complex areas of research that have not be synthesized in the past [12]. A scoping review also offers policy-makers easily accessible and comprehensive cost-effectiveness information and evidence regarding vaccines. Moreover, a review helps identify gaps in the vaccine economic evaluation literature and aids policy-makers spend their limited research funds more effectively and efficiently. We chose to conduct a scoping review rather than a systematic review because it allowed us to methodologically examine the breadth and depth of the work on economic evaluations of vaccines in a Canada, a highly multi-disciplinary area, while allowing for more flexibility than a systematic review [13]. The aims of our study were more consistent with the goals of a scoping review (e.g. to map the current state of the literature and summarize the breadth and depth of the research) in comparison to the goals of a systematic review (e.g. to summarize the evidence on the effectiveness of an intervention or treatment) [13]**.** The scoping review methodology allowed us to summarize a wide range of evidence including both grey (e.g. government reports) and peer-reviewed literature. Furthermore, rather than having a very specific and narrow research question, we asked a broad research question that encompassed all types of diseases, populations (target vs. universal) and interventions (i.e. types of vaccine) [13].

2.2.2. Identifying the research question

To further focus our research question – "What has been published regarding economic evaluations of vaccines in Canada?" – we decided to only consider active immunization,

vaccines that impact human health, and studies that focused on a Canadian population. To ensure comparability we chose to include only full economic evaluations, which we defined based on Drummond et al., 2005, and therefore, partial economic evaluations such as cost-outcome description studies and cost-minimization studies were not included [5,14]. Furthermore, to ensure the comprehensiveness of the review, we included both peer-reviewed and grey literature in our search. Only English-language articles were part of the final analysis.

2.2.3. Identifying relevant studies

To identify peer-reviewed articles we searched five databases relevant to both public health and economic evaluations: Embase, Medline, Global Health, Cochrane Library- specifically the Health Technology Assessment Database - and the NHS Economic Evaluation Database. No limitations were placed on the date and all databases were searched up until March 17th, 2015. We used a report-based expansion strategy centred on three essential keywords ('immunization' AND 'economic evaluation' AND 'Canada'). See **Appendix B, Table B.1.** for a full list of search terms used. After title, abstract and full-text review, the reference lists of all included articles were searched for relevant citations. We validated each database search for its efficiency and accuracy using ten articles that the reviewers identified as being highly relevant to the topic area. We compared the ten articles to the citations we identified during each database search.

To identify grey literature, we searched both the ProQuest Dissertation and Theses database along with key organizational websites related to health technology assessment, vaccination and economics in Canada, such as Canadian Agency for Drugs and Technologies in Health's (CADTH), the Health Quality Council from multiple provinces and Institute of Health Economics. We chose these organizations based on advice from a health sciences librarian, the opinion of experts in the field and the CADTH grey literature checklist [15]. In total we searched 25 potentially relevant websites and organizations.

2.2.4. Study selection

All eligible articles were imported into Microsoft Access 2010 for relevance screening and duplicates were removed. Independently, two reviewers evaluated the titles, abstracts and full-text of peer-reviewed articles by answering 'yes,' 'no,' or 'unsure' to each of the following questions (in no particular order):

1. Was the research conducted on a Canadian population? (i.e. presented Canadian-specific data or results?)
2. Was a full economic evaluation conducted (measured both costs and benefits, compared at least two interventions)?
3. Did the topic area relate to active vaccination or immunizations? (e.g. different types of vaccines, different schedules)?
4. Is a full-text available?
5. Is the article in English?
6. Were the results relevant to human health?

Furthermore, we excluded conference proceedings and any research that was presented in more detail elsewhere. During title, abstract and full-text screening of an article if the answer to any of the above questions was 'no' then the article was excluded; otherwise, the article was included in the next stage of analysis. We calculated Cohen's Kappa Coefficient at both the title, abstract and full-text screening stages to measure agreement between the two reviewers [16]. The reviewers resolved any disagreements through discussion and consensus. One reviewer screened the grey literature for inclusion or exclusion using the same process outline above; however, if the first reviewer was uncertain about the inclusion of an article it was given to the second reviewer. All the grey literature articles included in the final analysis were read by both reviewers.

2.2.5. Charting the data

Following full-text screening, the two reviewers charted each study chosen for inclusion using a standardized form designed to gather common and comparable information on each study. Data extracted included year of publication, region, targeted disease, type of economic evaluation (based on how benefits were measured), modelling type, herd immunity, target population, study perspective, time horizon, type of sensitivity analysis, comparator, the consideration of equity issues, general cost-effectiveness findings and stated conflict of interest(s). These variables were chosen based on CADTH's Guidelines for the Economic Evaluation of Health Technologies: Canada [17] and the World Health Organization's (WHO) Guide for Standardization of Economic Evaluations of Immunization Programmes [3] that outline information to include in an economic evaluation. We chose these two guidance documents as they were specific to Canada and to vaccines. The focus of our scoping review was

to summarize the range evidence and identify any gaps in the literature, rather than compare the results of the economic evaluation; therefore, we did not compare the articles based on quality. We charted each study's adherence to these guidelines and evaluated each study on whether they adequately (according to guideline protocols) presented six key principles that are considered essential for a well conducted economic evaluation. These six key principles included: time horizon, perspective, comparator, model-type and choice of economic evaluation (including justification for choice of model and economic evaluation), and if uncertainty in the results was fully accounted for through sensitivity analysis. This analysis gives policy-makers not only an idea of how economic evaluations are generally being conducted and presented in Canada, but also the effectiveness of their guidelines to inform research and whether the guidelines could be applied consistently across articles.

2.2.6. Summarising and reporting the results

Following data extraction, we used thematic analysis (i.e. determining and recording patterns or 'themes' within the articles) and descriptive statistics to analyze general trends and patterns in the data. We used chi-square tests to ascertain whether there was an association between stated conflicts of interests (i.e. at least one authors reported they were either currently working for the pharmaceutical industry or currently receiving funding) and their final cost-effectiveness recommendations (i.e. whether the authors stated the vaccine of interest was cost-effective or not, regardless of whether their determination was appropriate). Furthermore, we studied the association between the publication year (i.e. <2010 or ≥2010) and the studies adherence to the six key principles of an economic evaluation discussed in the WHO and CADTH guidelines (i.e. adhered to guidelines or not). We also examined the association between publication year (i.e. <2010 or ≥2010) and choice of modelling type (i.e. static vs. dynamic). We chose 2010 as the cut off year as it provided adequate time after the publication of the WHO (2008) and CADTH (2006) guidelines for authors to incorporate the recommendations in their research. Finally, we calculated the number of studies that took place prior to licensure of the vaccine in Canada, between licensure and the implementation of the vaccination program being studied, and those that occurred after the implementation of the vaccine in the region considered in the study. We were particularly interested in economic evaluations that aimed to re-evaluate the cost-effectiveness of the vaccine post-implementation and therefore included retrospective data (ex-post).

2.3. Results

Following the database search and the removal of duplicates, 908 peer-reviewed articles remained to be screened. Based on title and abstract screening we eliminated 792 articles, leaving 116 articles for full-text review, of which 55 were included in the final analysis (**Figure 2.1**). All ten 'original' studies chosen as being highly relevant to the research and used to validate the search methods were identified in each of the database searches. There was substantial agreement between the two reviewers; Cohen's Kappa Coefficient was 0.81 for the title and abstract screening and 0.85 for the full-text screening. The reviewers reached consensus in all cases of disagreement.

Following the grey literature search and title screening we retrieved 38 potentially relevant studies and dissertations from 25 websites and the ProQuest Theses database, of which five were retained in the final analysis. Sixty peer-reviewed and grey-literature studies were included in the final scoping review analysis (**Figure 2.1**).

2.3.1. Summary of studies included in the review

The number of articles by year of publication, region, disease, type of economic evaluation, modelling type, consideration of herd immunity, perspective, time horizon and sensitivity analysis were summarized (**Table 2.1**). The number of economic evaluations of vaccines increased from 1988 to March 2015; 66.7% of economic evaluations were published within the last ten years (i.e. since 2005) (**Figure 2.2**). Most studies focused on Canada in general (58.3%), with Quebec (13.3%), Ontario (10.0%) and British Columbia (8.3%) producing the most province-specific vaccine economic evaluations. Economic evaluation of vaccines in Canada considered 20 different diseases including, from most common to least common - influenza (pandemic-2 and seasonal-8) [18–27], Human Papillomavirus (HPV) [28–36], pneumococcal [37–45], pertussis [46–50], meningitis A,C, Y and/or W135 [51–55], hepatitis B [56–60], varicella [61–63], measles, mumps and/or rubella [64–66], herpes zoster [67,68], rotavirus [69,70], rabies [71], hepatitis A [72], tetanus [73], hepatitis C [74], meningitis B [75], group B streptococcus [76], and *Escherichia coli* [77] (**Figure 2.2**).

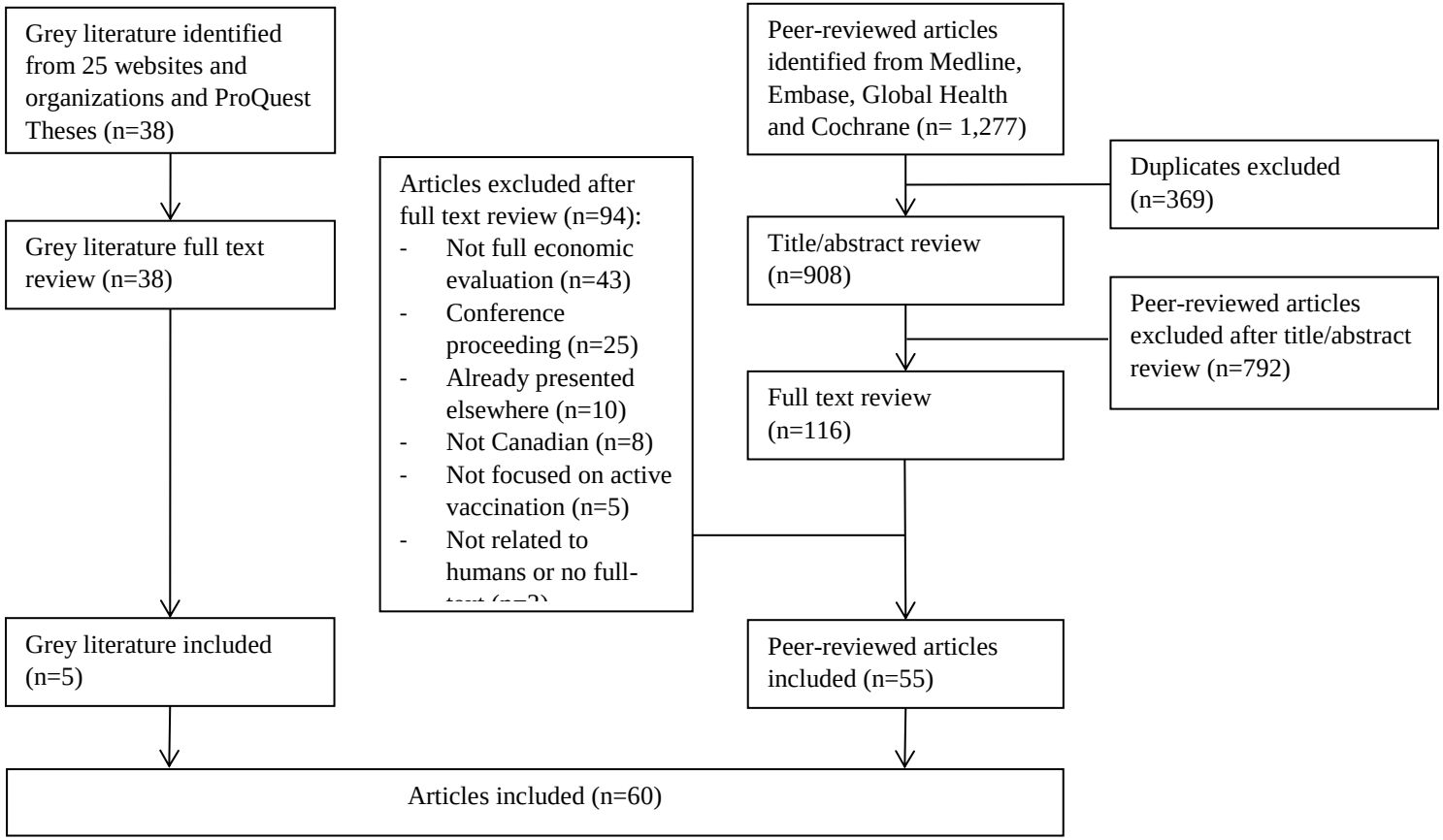

Figure 2.1. Flowchart for the identification and selection of studies included in the scoping review

Table 2.1. Summary descriptive statistics and variable frequency for 60 vaccine economic evaluations

Variable	Number of studies included	Percentage of total (n=60)
Source		
Peer-reviewed	55	91.7%
Grey-literature	5	8.3%
Year of publication		
Before 1995	3	5.0%
1995-2004	17	28.3%
After 2005	40	66.7%
Region		
Canada	35	58.3%
Atlantic*	2	3.3%
Quebec	8	13.3%
Ontario	6	10.0%
Manitoba	1	1.7%
Saskatchewan	0	0.0%
Alberta	3	5.0%
British Columbia	5	8.3%
Territories**	0	0.0%
Disease		
Influenza	10	16.7%
HPV	9	15.0%
Pneumococcal	9	15.0%
Pertussis	5	8.3%
Meningoccocal A,C,Y or W135	5	8.3%
Hepatitis B	5	8.3%
Varicella	3	5.0%
Measles, Mumps or Rubella	3	5.0%
Herpes Zoster	2	3.3%
Rotavirus	2	3.3%
Rabies	1	1.7%
Hepatitis A	1	1.7%
Tetanus	1	1.7%
Hepatitis C	1	1.7%
Meningoccocal B	1	1.7%
Group B Streptococcus	1	1.7%
Escherichia coli	1	1.7%

*Includes the provinces of New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador.

**Includes the territories of Yukon, Northwest Territories, and Nunavut.

Table 2.1. Continued

Variable	Number of studies included	Percentage of total (n=60)
Type of Economic Evaluation		
Cost-utility	37	50.0%
Cost-effectiveness	30	40.5%
Cost-benefit	7	9.5%
Modelling Type		
Simple Tree	16	21.6%
Static cohort	25	41.7%
Dynamic cohort	7	11.7%
Individual-based	5	8.3%
No modelling (e.g. RCT, simple calc.)	7	11.7%
Consideration Herd Immunity		
Yes	25	41.7%
No	35	58.3%
Time Horizon		
≤1 year	7	11.7%
>1-29years	14	23.3%
30-79	8	13.3%
80+	25	41.6%
Not stated	6	10.0%
Perspective		
Individual/Familial	4	6.7%
Healthcare pay	35	58.3%
Public Pay	10	16.7%
Societal	28	46.7%
Not stated	8	13.3%
Sensitivity Analysis		
Yes-deterministic	53	88.3%
Yes-probabilistic	23	38.3%
No	5	8.3%
Alternative/comparator		
No vaccine	40	66.7%
Different schedules of vaccines	16	26.7%
Different types of vaccines	16	26.7%
Conflict of Interest		
Yes	28	46.7%
No	32	53.5%

The most popular type of economic evaluation used in Canadian studies was cost-utility analysis (50.0%); although, it was often combined with cost-effectiveness analysis. The majority of the cost-utility analyses used QALY as the outcome measure. More than half of the studies used static modelling (e.g. simple tree or static cohort) (63.3%). Most studies used a life-time horizon (i.e. 80+ years) (41.6%), with a healthcare payer (58.3%) or societal perspective (46.7%), often combining the two perspectives. Researchers employed a wide range of comparators (**Table 2.2**). The vaccine of interest was compared to no vaccine in 66.7% of studies. The evaluation compared different ways of administering the vaccine (e.g. different schedules or target populations) in 25.0% of studies. Different types of vaccines (brands or antigen formulations) for the same disease were compared in 26.7% of studies, with some studies employing more than one type of comparator. Most studies (86.7%) evaluated publicly-funded vaccines that were included on at least one provincial immunization schedule (**Table 2.2**). Finally, only six studies in our analysis had a discussion of equity, which mainly focused on the fact that they were unable to address issues of equity within their analysis.

2.3.2. Factors associated with reporting practices and study findings

In reports where there was a stated conflict of interest, the authors were more likely to assert the vaccine of interest was cost-effective relative to the comparator (OR= 7.36; CI= 1.04, 17.8; p-value=0.04) than in reports with no reported conflict. Furthermore, studies published from 2010-2015 were more likely to follow the six key principles in the WHO and CADTH reporting guidelines compared to those studies published before 2010 (OR= 4.58, CI= 1.33, 18.7, p-value = 0.01) (**Figure 2.3**). However, there was no difference in the type of model employed before 2010 compared to 2010-2015 (OR= 3.05; CI= 0.66, 16.8; p-value=0.16). All of the five individual-based models were published in the last five years [22,29,31,32,71].

Most studies (66.7%) were completed before the vaccine program of interest was implemented in Canada with 8.3% before the vaccine was licensed. One in four studies (25.0%) were completed after the vaccine program was implemented. Only five post-implementation studies (8.3%) were ex-post and therefore evaluated vaccination strategies using retrospective data on costs and effectiveness [22,23,44,49,53].

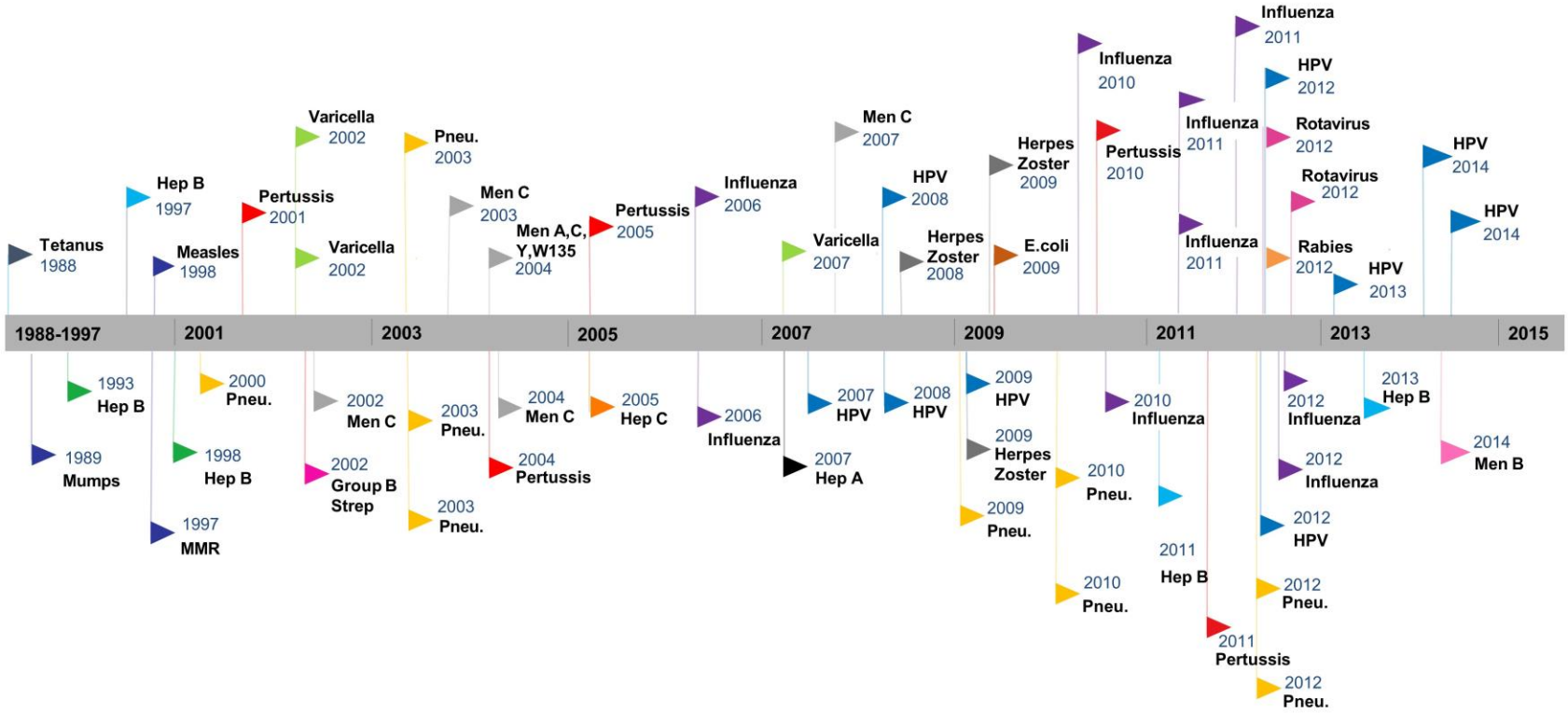

Figure 2.2. Timeline of Canadian economic evaluations of vaccines

*Each flag colour in the above figure represents a different disease.

Table 2.2. The vaccine comparators and schedules used in each economic evaluation

Vaccine	Number of studies- No vaccine	Number of studies- Type of vaccine	Number of studies- Vaccine program**	Funding and Target Population***
Escherichia coli	1 (0/1)*	-	-	Private
Group B streptococcus	1 (1/1)	-	-	Not yet available
Hepatitis A	-	1	-	Private
Hepatitis B	5 (3/5)	-	1	Public-Universal
Hepatitis C	1 (1/1)	-	-	Not yet available
Herpes Zoster	2 (2/2)	-	-	Private
HPV	7 (7/7)	4	2	Public-Universal
Influenza- (Seasonal & H1N1)	6 (5/6)	1	4	Public-Universal/Targeted
Measles or Mumps or MMR	2 (2/2)	-	3	Public-Universal
Meningococcal A, C, Y, W135	2 (1/2)	2	1	Public-Universal
Meningitis B	1 (0/1)	-	-	Public-Targeted/Private
Pertussis	1 (1/1)	2	2	Public- Universal
Pneumococcal	4 (4/4)	4	1	Public-Universal
Rabies	1 (1/1)	-	-	Private
Rotavirus	2 (2/2)	2	-	Public-Universal
Tetanus	1 (1/1)	-	-	Public-Universal
Varicella	3 (2/3)	-	1	Public-Universal

*Ratio represents the number of studies that found the vaccine was cost-effective compared to no vaccine.

** For example: schedule, booster dose, universal vs. targeted.

***Funding and target population for vaccines as of March 2015.

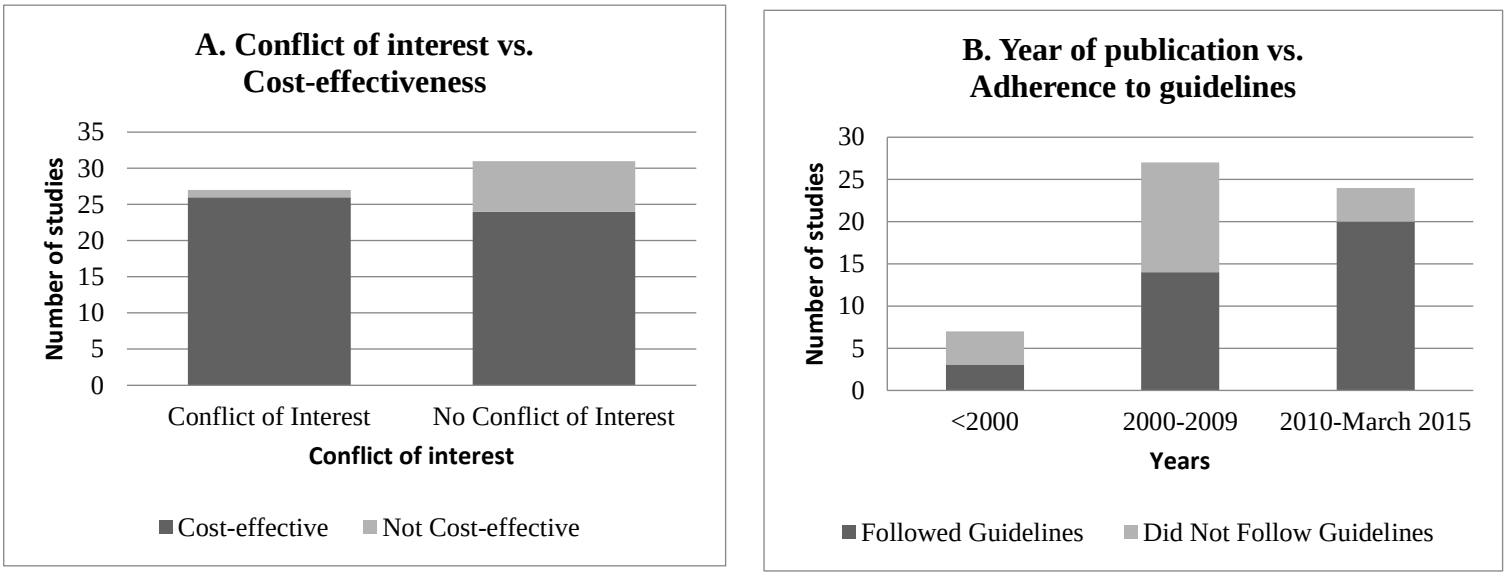

Figure 2.3. Comparison of number of economic evaluations by criteria of interest

2.4. Discussion

In recent years, the number of economic evaluations on health interventions have increased in Canada and worldwide [17,78]. The results of our scoping review are consistent with these trends, with 50.0% of the economic evaluations of vaccines in Canada being produced in the last five years [17,78]. There are many explanations for this increase in economic evaluations, including increasing pressures on the budgets of healthcare systems, as well as the advent of new, complex and more expensive vaccinations [78,79]. Therefore, it is perhaps unsurprising that the influenza, pneumococcal and HPV vaccines represented almost 50.0% of the economic evaluations, as the immunization programs for these diseases, including the schedules, vaccine-type, administration techniques and target populations have all changed over the last few years. For instance, recently decision-makers have raised questions surrounding the cost-effectiveness of male HPV vaccination, using the modified live intranasal influenza vaccine in children between two and 17, and which pneumococcal vaccine (i.e. PCV13, PCV10 and PCV7) would give the best value for the money, particularly considering the impact of serotype replacement and otitis media [27,29,31,32,37,39,40,45].

Most economic evaluations focussed on publicly-funded vaccines that were part of at least one provincial immunization schedule. A very small proportion of the research was done on privately-available vaccines, such as travel (e.g. yellow fever, Japanese encephalitis) and

workplace vaccines (e.g. rabies) [71,77]. Furthermore, there is only a small amount of research on vaccines not yet available or licensed in Canada (e.g. chlamydia, herpes simplex), with some notable exceptions (i.e. hepatitis C and Meningococcal B) [74,75]. Anticipatory economic evaluations can provide essential information on the needs for additional research and investment.

In Canada, most of economic evaluations occur after the vaccine has been licensed but before the implementation of the vaccine program in the population (ex-ante). These ex-ante studies are important as they provide decision-makers with an estimate of the value of instituting a new vaccine and the costs and benefits of different vaccination programs (e.g., privately, targeted, universal). However, ex-ante evaluations are difficult to perform as country-specific effectiveness and cost data is often lacking before implementation, and the ability to predict the vaccination impact, particularly herd effects, is limited [80]. For instance, prior to vaccine implementation it is difficult to predict the real market price of a vaccine, which can vary dramatically in space and time. Therefore, there is a need to evaluate whether existing vaccination programs are good value for their cost, especially because effectiveness and cost data can change drastically over time [80]. These ex-post studies allow researchers to validate estimates of costs and outcomes from pre-implementation evaluations, and potentially improve future studies [80].

However, we saw little evidence of ex-post economic evaluations. For instance, the costs and outcomes of the varicella vaccine ex-post have not been compared with the two inconclusive studies conducted ex-ante (69,70). In fact, only five studies were identified where the goal was to determine the efficiency of a mass immunization after its implementation in the population [22,23,44,49,53]. This gap in the literature may be partially due to the politics of de-implementation, especially as scaling back an intervention is a complicated process in health care and often met with resistance. However, the lack of retrospective research has left many unanswered questions, such as ‘How good are Canadian economic evaluations at predicting the cost-effectiveness of vaccines and should these studies inform our policy-making?’ This gap in the literature may be partially due to a lack of industry willingness to fund ex-post studies or because of noted methodological limitations, including issues with estimating the ‘no program’ scenario, attributing decrease in disease to vaccination and predicting future benefits [80]. However, Newall et al. (2014) [80] has identified a variety of approaches that help address these

issues, noting that as retrospective studies become more important and frequent, it would be beneficial to increase the guidance available to researchers undertaking such analyses. In the future, a clearer understanding of the accuracy of economic evaluation predictions could help researchers improve research techniques and potentially increase the efficiency of current vaccination programs.

Most of the studies in this review compared the vaccine of interest to no vaccination. While this is an essential initial comparison, once a vaccine is well-established, there are other questions that economic evaluations can help answer, including questions about vaccine programming and scheduling. In Canada, healthcare is primarily under provincial/territorial (not federal) jurisdiction and as a result there is a diversity of vaccine programs, technologies and schedules throughout the country. To date there have been no reported studies of which vaccination programs are most efficient or cost-effective, or whether these differences are justifiable due to the epidemiology and costs in different Canadian regions.

The use of modelling in economic evaluation of vaccines has increased in the last few years. Most studies continue to employ static models (e.g. decision tree, Markov processes) as compared to dynamic models (e.g. system dynamics, individual-based models). In dynamic models, the risk of infection can change over time. There has been no apparent increase in the application of dynamic modelling and no relationship between modelling type and year of publication [81]. Although dynamic models are not always necessary to represent vaccine preventable diseases (e.g. tetanus, Herpes Zoster), they allow for the intrinsic consideration of vaccine externalities (herd immunity, shifts in age of infection and serotype replacement). Consideration of externalities is limited in the Canadian literature, with fewer than half of studies in our review considering herd immunity. Failure to include the impact of herd immunity can significantly underestimate the effectiveness of a vaccine [81]. An increase in dynamic modelling, where relevant, could improve the accuracy of economic evaluations of vaccines and should be an area of future research.

Individual-based models are, however, becoming increasingly popular in economic evaluations [22,29,31,32,71]. These models have the advantage of being able to replicate individual-level behaviour and interactions (e.g. transmission, risk behaviours, disease history), which may have substantial impacts on the economic evaluation. Individual-based models not only intrinsically account for the impact of herd immunity but also help researchers study the

influence of key subsets of the population. Three separate economic evaluations on HPV used a common individual-based model called HPV-ADVISE to estimate the costs and benefits of different vaccination strategies and scenarios in Canada [29,31,32]. The HPV-ADVISE model informed HPV vaccine policy-making regarding the cost-effectiveness of various vaccine types (bivalent versus quadrivalent versus nine-valent), catch-up programs, type replacement, schedules (ages, number of doses), as well as male-vaccination. HPV-ADVISE is an example of the power and flexibility of individual-based modelling and how information sharing can improve economic evaluation research and therefore the policy-informing power of these types of studies. However, there are also trade-offs to consider with dynamic models, specifically individual-based models, as they are often more complex, time consuming and can require more fine-grained data, potentially impacting the reliability and timeliness of the results.

Authors' choice of the time horizon and discount rate can significantly impact the outcomes of an economic evaluation. As is noted in many guidelines for economic evaluations, for accurate analysis the chosen time horizons must encompass all costs and benefits of a policy decision [17]. However, as we saw in this analysis many economic evaluations adopt a shorter than necessary time horizon (e.g. economic evaluations adopting the same time horizon as a clinical trials), creating the possibility of a time horizon bias, wherein the cost-effectiveness of an intervention is often underestimated. Another important element of economic evaluations that can significantly impact the outcomes of a cost-effectiveness analysis is the perspective and therefore, which costs are considered in the analysis. It is essential that economic evaluations clearly justify their choice of perspective and discuss the costs not considered, however a complete discussion of choice of perspective was often missing in the studies of our analysis. However, as recommended in the CADTH guidelines [82], studies are starting to adopt a two - perspective approach, where they not only consider the economic benefits and cost from a narrower view point (e.g. healthcare payer) but also using the most comprehensive approach (i.e. societal perspective). Reporting of time horizon and study perspectives in economic evaluation of vaccines must improve to ensure the transparency of complex analyses and to provide the details necessary for informed decision-making.

In our review only six articles included some assessment or discussion of equity in their analysis. Lack of equity considerations and inability to account for equality in resource allocation analyses are common criticisms of economic evaluations [83]. Debate continues around whether

economic evaluations have the responsibility to consider equity; however, the lack of information on the differential impact of interventions often means policy-makers are hesitant to use the results of economic evaluations [83]. In recent years there have been a number of methodological advancements to help economists account for equity as part, or as an extension, to their cost-effectiveness analysis (e.g. extended or distributional cost-effectiveness); however, the use of these tools is still limited [84]. As the field of economic evaluations of vaccines continues to grow it is important that these studies consider and discuss how their findings may have an impact on the equity of health care delivery and health outcomes.

Research shows that guidelines for economic evaluation from non-governmental organizations, governments and journals can help increase transparency and reliability of these studies [78]. In fact, one of the main reasons the WHO created guidelines for economic evaluation of vaccines in 2008 [3] was to address the limitations they observed in evaluations reported prior to 2005, and to enhance standardization and comparability between studies [2]. Both Baladi et al. (1998) and Neumann et al. (2005) discovered a growing adherence to recommended practices in cost-effectiveness and cost-utility analyses worldwide and in Canada, which they attributed to stricter journal protocols and guidelines in publishing these studies [78,85]. Our results further support these findings indicating that since the publication of WHO and CADTH guidelines there has been an increase in the standardization of the methods used in economic evaluation and in the transparency and reporting of the research in Canada [3,17]. Although, we noted a change in the consistency of reporting following the introduction of the guidelines, there remained certain study elements commonly omitted, such as the study perspective, modelling technique description and time-horizon. The large number of assumptions and parameters used in economic evaluations make reporting guidelines essential, as simple changes to the perspective adopted, discount rate or time horizon chosen can have a major impact on the results [6]. Therefore, the transparency and reliability of these studies should continue to improve, and the guidelines must be continually updated to ensure that the results are both useable and translatable.

The use of national guidelines and publishing protocols is particularly relevant and important to our sample of articles, as just under half the studies had reported conflicts of interest and these studies were significantly more likely to find the vaccine of interest cost-effective.

Therefore, transparency and consistency in economic evaluations are essential to ensure policy-makers can use the results to make accurate and unbiased decisions

This study had a number of limitations. First, we were unable to search for or include articles in French, and therefore may have missed contributions to the economic evaluation literature, especially as Quebec was the most prolific areas in the production of economic evaluations of vaccines. Second, only one reviewer was able to screen the grey literature articles for inclusion. Nevertheless, all final decisions were discussed between the two reviewers to ensure agreement about all studies included in the analysis. Finally, we did not compare the results of the economic evaluations because we had included articles for a variety of diseases and with a wide range of quality.

2.5. Conclusions

To date economic evaluations of vaccines in Canada have not been summarised or reviewed, potentially limiting the influence these studies have on policy-making. This scoping review acts as a guiding document for policy-makers and researchers, to provide easy access to essential information about vaccines. Our scoping review outlined many gaps in the literature, including the lack of studies on various privately-available vaccines, different vaccination schedules and programs, and the shortage of ex-post implementation economic evaluations. Furthermore, we identified important trends in the literature, including an increasing number of economic evaluations on vaccines and a focus on newly-available vaccines.

We found some weaknesses in the literature, including the limited use of dynamic modelling and consideration of herd immunity, the significant association between declared conflicts of interest and an increased frequency of a positive cost-effectiveness result, as well as the under-reporting of time-horizon, perspective and modelling type. However, the scoping review outlined some key strengths of the Canadian literature, including an increase in the application of individual-based modelling techniques. Furthermore, the implementation of national guidelines appears to have had an impact on the standardization and transparency of economic evaluation in Canada and remains an important consideration for countries without similar guidelines. As more countries start to map this literature and analyse the trends and limitations, then comparisons between countries, their economic evaluation literature and their vaccination programs; could provide valuable input for improving the quality and usefulness of economic evaluations of vaccines.

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CHAPTER 3- BACKGROUND ON CHICKENPOX AND SHINGLES

The scoping review in the previous chapter identified several gaps and limitations in the Canadian economic evaluations of vaccines literature, including in studies that focus on chickenpox and shingles. All the economic evaluations of universal chickenpox vaccination in Canada were conducted prior to the vaccine's implementation into any provincial vaccination schedule. Furthermore, while many chickenpox economic evaluations used dynamic models, they did not employ an agent-based infectious disease model, which is a tool that could further our understanding of chickenpox disease and vaccination, including the costs and outcomes associated with both. This chapter provides context for the last three articles (**Chapters 4, 5, and 6**) of this thesis, including background on the varicella zoster virus (VZV), the immune response to VZV infection, transmission and epidemiology of chickenpox and shingles, as well as the pathogenesis, diagnosis and treatment of these diseases. This chapter summarizes the history of the chickenpox vaccination both worldwide and in Canada, along with current research on how universal vaccination affects population-level chickenpox and shingles outcomes. Furthermore, this chapter discusses several types of infectious disease models, including agent-based modelling, which is employed in the following chapters to estimate the epidemiology and cost-effectiveness associated with chickenpox vaccination.

3.1. Varicella zoster virus and immunology

Varicella zoster virus (VZV) is an enveloped double stranded DNA virus that can cause two distinct diseases, varicella (chickenpox) and herpes zoster (shingles). Chickenpox is the primary infection with VZV and generally occurs in childhood. However, as a member of the Herpesviridae family, during primary infection VZV has the capacity to travel to the sensory ganglia and remain latent in neurons for years. Reactivation of latent VZV can cause a secondary infection in the form of shingles.

VZV spreads almost entirely from cell-to-cell making cell-mediated immunity (CMI) particularly important in the development of long term immunity to VZV [1]. While humoral immunity may also play a role, it is not sufficient to ensure protection. Patients with compromised CMI (e.g. HIV/AIDS) are at an increased risk of developing VZV infections and more severe chickenpox [1,2]. An increased risk of shingles in CMI-impaired individuals supports the hypothesis that immunological control is important in the suppression of VZV reactivation. In fact, the decline of CMI with age is one of the theories why age remains the main risk factor for shingles infection. While there is only one serotype for chickenpox, there are various genotypes, which have a distinct geographical distribution [1].

3.2. Chickenpox disease and epidemiology

Chickenpox is characterized by an itchy, sometimes painful generalized vesicular rash, often coinciding with malaise and fever, with symptoms continuing for 5-7 days. Other symptoms include, anorexia, headache, and mild abdominal pain. Although, in healthy children chickenpox is generally a self-limiting disease, there are a wide variety of possible complications. Secondary bacterial infection (e.g. group A streptococcal infection) is the most common complication in childhood but other complications include acute cerebellar ataxia, encephalitis, and congenital varicella syndrome [3]. Severe illness and/or complications are more common in certain risk groups, including, pregnant woman, neonates, infants, and immunodeficient patients, particularly those with cellular immune deficiencies [3,4]. Furthermore, chickenpox can be more severe in adolescence and adulthood. Generally, once an individual has had chickenpox they remain immune for life [4]. However, some evidence shows that subclinical reinfection, also known as endogenous boosting can occur, and one theory posits that this increase an individual's immunity to future virus reactivation.

3.2.1. Chickenpox diagnosis and treatment

Diagnosis of chickenpox is usually done using both clinical and epidemiological evidence, including the identification of the characteristic vesicular rash, along the individual's history of chickenpox and their recent contact with a chickenpox or shingles case [1]. Lab testing of vesicles or body fluids using PCR to identify viral DNA is becoming the favoured diagnostic test, as it is generally considered the most sensitive, although it is not routinely done on patients [1]. Serological testing for VZV antibodies is often used to assess health care workers' immunity to chickenpox; however, they have yet to find a true measure of protection as the absence of antibodies in a vaccinated individual does not reliably mean they are at risk of disease [1].

While most cases of chickenpox are treated with supportive care, antiviral therapies do exist for chickenpox infections. Antivirals may decrease the severity and reduce recovery time for chickenpox infection; however, they do not appear to have an impact on virus transmission [1]. Therefore, these medications are generally not prescribed for a typical chickenpox case but are used for immunocompromised individuals who contract chickenpox and for more severe cases of shingles [1]. Other medical options to help prevent or attenuate chickenpox infection include post-exposure prophylaxis. Chickenpox vaccination given within 5 days of exposure is commonly used for post-exposure prophylaxis. While it shows inconsistent results for the prevention of disease, it is highly effective in limiting disease severity. Another option for post-exposure prophylaxis is passive immunization with immune globulin, which, is the recommended method to limit the severity of the infection in immunocompromised individuals, neonates, premature infants and pregnant woman [5]

3.2.2. Epidemiology chickenpox pre-vaccine era worldwide

Prior to vaccination, chickenpox was endemic worldwide, with the majority of individuals being infected by mid-adulthood [1]; however, the rate of chickenpox infection and the age-distribution differed by temperate and tropical climates [2]. In temperate climates pre-school children had the highest burden of chickenpox infection, with 90% of individuals having been infected by adolescence [4]. In comparison, in tropical climates there was a higher mean age of infection along with a higher percent of adults who are susceptible [1,6]. Theories as to why we observed these differences in VZV epidemiology between temperate and tropical

climates include the fact more children attend school and day in temperate climates and for longer [6].

In Canada, prior to chickenpox vaccination, there were approximately 350,000 chickenpox cases per year, or 11.9 cases per 1,000 persons [7]. Periodic outbreaks tended to occur at a cycle of 2-5 years, with 90% of children infected by age 12 [7]. In the United Sates there were approx. 4.1-5 hospitalization per 100,000 persons and 0.4-0.6 deaths per million persons per year [1]. At the same time, chickenpox contributed to a considerable number of school and work days missed [8]. All these factors, including hospitalization costs, general practitioner costs and productivity loss contributed to chickenpox's substantial economic impact [8,9].

3.3. Shingles disease and epidemiology

3.3.1. Reactivation and boosting

Shingles is a disease caused by the reactivation of the VZV in individuals previously infected with chickenpox. Following primary infection of VZV, the virus can move to the sensory ganglia and remain latent there for future reactivation as shingles [2]. Reactivation of VZV causing shingles is generally associated with a decrease of VZV cell-mediated immunity (VZV-CMI) associated with ageing and senescence. Research shows that CMI is the key response to controlling VZV in the host, as viral spread occurs from infected cell to uninfected cell [1]. For instance, those with impaired CMI have higher rates of shingles and chickenpox, and the infection is often more serious in these cases [1]. The current assumption in the literature is that immunity to VZV wanes over time and once it reaches a certain undefined critical threshold, VZV has the possibility to reactivate in the form of shingles. Other factors have been shown to effect immunity to VZV, including changes in mental health such as depression and stress, concurrent infection, trauma to the dermatome, gender and possibly race [2].

In parallel to the natural waning of VZV-CMI immunity, one theory posits that exogenous boosting of VZV-CMI is a determinant of shingles reactivation [10]. According to Hope-Simpson [10] exogenous boosting occurs when a chickenpox immune individual is exposed to a case of chickenpox or shingles. Multiple studies show that populations commonly exposed to children and chickenpox (e.g. pediatricians, mothers) have lower shingles incidence rates than the general population; however, these findings are inconsistent [1,11,12]. Furthermore, shingles vaccine administered to chickenpox immune individuals induces a

substantial boost in VZV-CMI; however, the length of the boost (i.e. time protected from shingles) remains unknown [13]. At the same time, some studies suggest an individual's immune system may react to an attempted reactivation of VZV, in effect boosting the immune system and preventing future reactivation, this event is known as endogenous boosting [14].

3.3.2. Shingles diagnosis and treatment

Shingles is generally a more serious disease than chickenpox, causing significant radicular pain that lasts for a prolonged period, even years in some cases. Shingles is characterized by a vesicular rash, similar to that seen in chickenpox; however, it is usually only seen along a single dermatome. Shingles can occur in the absence of a rash, although it is rare. Other symptoms include, itching and prodromal pain that varies by consistency, character (boring, aching, shooting) and severity by case [2]. Shingles is also associated with multiple complications. One of the most frequent and severe complication is post-herpetic neuralgia (PHN), which is prolonged neurogenic pain (ranging from >30-90 days) that is often debilitating [15]. Other complications include, sight-threatening eye infections, neuromuscular disease (e.g. Guillain-Barre Syndrome), secondary bacterial infection, and nerve palsies [15].

Like chickenpox, diagnosis of shingles is usually done clinically with the appearance of the rash accompanied by prodromal pain. Treatment for shingles includes antiviral therapy, for both healthy and immunocompromised patients, and should be started as soon as possible. Pain management, including the use of strong analgesics, is also a key factor in the medical management of shingles [4]. The number and costs of antivirals and analgesics prescriptions for shingles have increased in the past few years [16].

3.3.3. Epidemiology of shingles worldwide and in Canada

Studies from across the world, including Canada, Japan, US, Taiwan and Israel estimated an overall age-adjusted incidence rate of shingles between 3.4 and 5.0 cases per 1,000 persons prior to chickenpox vaccination. Shingles rates can differ significantly by country, for instance in Europe the rate of shingles varied from 2 to 4.6 cases per 1,000 person-years with no particular geographical trend [17]. Estimates in Canada average around 4.6 shingles cases per 1,000 healthy persons per year, with a lifetime risk of 15-20% [4,18,19]. A few studies have shown that the incidence rate of shingles had been steadily increasing in the years leading up to chickenpox vaccination [20]. For example, a study from Alberta found that the rate of shingles increased

from 2.7 to 4.3 cases per 1,000 persons per year between 1986 and 2002 [21]. While this study did not adjust for age, Edgar et al. (2007) [18] and Marra et al (2006) [22] found similar increases in the age-standardized incidence rate of shingles in Canada. Adjusting for age is important as the incidence and severity of shingles does increase with age, for instance the rate of infection for persons over 65 (8-11 cases per 1,000 persons) is two to three times higher than the overall age-adjusted incidence rate [4]. Therefore, approximately half of adults who reach 85 years old suffered at least one episode of shingles [4]. Although shingles does not spread through contact, shingles can represent a mode of VZV exposure to individuals susceptible to chickenpox, and therefore can introduce VZV into small communities unable to sustain endemic chickenpox transmission.

3.4. Chickenpox and shingles vaccination

All chickenpox vaccines are developed using the Oka strain of the VZV and were originally tested during clinical trials completed in the 1970s [1]. Currently licensed vaccines include monovalent vaccines, Varivax (Merck) and Varilrix (GSK) and combination vaccine measles, mumps, rubella, varicella (MMRV), such as Proquad (Merck) and Priorix-Tetra (GSK) [1]. All vaccines currently licensed are live-attenuated and administered subcutaneously. Chickenpox vaccines are considered very safe; however, adverse side effects do occur. The most common adverse events are minor, and include tenderness and redness, fever and mild rash [1]. The risk of febrile seizures in 12-months-old infants who receive the MMRV combination vaccine was slightly but significantly higher than those who receive MMR+V (MMR and varicella separately) [23]. All the chickenpox vaccines are generally considered safe and effective in immunocompromised individuals. However, there is the potential for severe reactions, including skin rash and fever, and the vaccine is sometimes contraindicated for this group.

3.4.1. Chickenpox vaccination efficacy and effectiveness

Following chickenpox vaccination, most healthy children demonstrate an IgG antibody response, with one study showing approximately 84% of children seroconverted following first dose vaccination [24]. This is comparable to a larger study of primary vaccine failure in the US which found 24% of individuals who received one-dose chickenpox vaccination had no detectable antibody to the virus [25]. These two studies, together with other estimates of

seroconversion and primary vaccine failure, suggests approximately 9% to 24% of healthy children are not fully protected following initial chickenpox vaccination [1,26,27]. Two-dose chickenpox primary vaccination failure is likely very low, with one randomized control study demonstrating a 94.9% efficacy against any disease and 99.5% effective against severe/moderate disease following vaccination with MMRV [28].

In comparison, the importance of secondary-vaccine failure or waning of immunity continues to be debated in the literature [29]. Chaves et al. [30] examined the rate of breakthrough chickenpox in the 10 years since implementation of the vaccine program in the US and found the rate of breakthrough significantly increased with the time since vaccination, suggesting an element of waning of vaccine immunity. However, while studies have confirmed these findings others have found that vaccine-derived antibodies persist in the individual long-term. Furthermore, it is difficult to determine whether the persistence of immunity is due to re-exposure to wild-type disease as many of these studies were conducted while chickenpox was still circulating in the population [4]. If secondary vaccine failure does occur, further study is needed to determine the rate at which it occurs, the significance of re-exposure events and the importance of a second dose. A systematic review of the real-world chickenpox vaccine effectiveness suggested that single dose vaccination had a median effectiveness of approximately 83% against disease of any severity, although it ranges dramatically from 20% to 100% when comparing among individual studies [4]. However, this review also estimated the effectiveness in preventing moderate disease was very high at 95% and found complete protection against severe disease [4].

3.4.2. Chickenpox vaccine globally and in Canada

In the United States one-dose chickenpox vaccination was licensed in 1995 and shortly after was first recommended for routine use in children. In 2007 the Advisory Committee on Immunization Practices shifted their recommendations to a 2-dose schedule (12-15months and 4-6 years) [5,31]. Canada licensed the Oka strain chickenpox vaccination in 1998, and Prince Edward Island became the first province to implement universal vaccination in 2000 [32,33]. By 2007 all provinces had a routine one-dose chickenpox vaccination program. However, in 2011 the Canadian Pediatric Society recommended a switch to a two-dose schedule, citing breakthrough cases, continued outbreaks and concern the disease was shifting to older populations where it is often more severe [34]. At the same time, many countries, including most

European countries, have decided to delay the implementation of universal chickenpox vaccine in their routine schedules, often citing cost-effectiveness, the generally low severity of chickenpox infections and the potential impact on shingles rates [35].

Currently, while most provinces and territories have a two-dose vaccine program, the schedules implemented by province/territory varies widely across Canada, with eight different schedules amongst the 13 provinces/territories [36]. These schedules differ in the timing of the first dose (12 to 15 months), the timing of the second dose (e.g. 18 months vs. 4-6 years), the type of vaccine given at the first and second dose (varicella vs. MMRV) and the availability of catch-up doses [36]. In 2001, Alberta became one of the first provinces to implement a routine chickenpox vaccine program with Varivax® for children aged 12 months [37]. In 2010, they switched to the combined vaccine MMRV (Priorix-Tetra®) for vaccination at 12 months and proceeded to add a second dose of MMRV at 4-6 years in 2012 [37].

3.4.3. Burden of illness post-chickenpox vaccination

Following chickenpox vaccine implementation in the US chickenpox incidence decreased by over 90%, while simultaneously precipitating an 88% reduction in hospitalizations, and 74% to 92% fewer deaths associated with chickenpox [38–40]. Similar declines were seen in Canadian provinces following the initiation of chickenpox vaccination. For instance, eight years following the introduction of chickenpox vaccination in many provinces Waye et al. [41] found that chickenpox hospitalization decreased by up to 86% nationally (86% in children aged 1-4 and 46% in adults 40-59). Simultaneously, Wormsbecker et al. [42] found annual declines in office visits ranging from 7.7-9.1% in Ontario between 2004 and 2011. These findings demonstrate the effectiveness of chickenpox vaccination to reduce the medical outcomes associated with chickenpox, as well as illustrate the ability of herd immunity to diminish the impact of chickenpox in non-vaccinated populations. However, outbreaks and breakthrough cases continue to occur in Canada [34,43,44].

Like many other vaccine-preventable diseases, diagnosis of breakthrough infection for chickenpox is difficult, as symptoms are often less severe, and individuals may not have the characteristic rash. Lab-diagnosis of chickenpox infection can also be hampered by vaccination as the evidence shows that established lab tests used to identify wild-type chickenpox are not accurate tests for identifying vaccine-VZV [15]. Estimating the number of individuals with breakthrough illness is also difficult as the cases are quite mild and therefore individuals may not

seek medical attention. However, estimates suggest that around 3-9% of total chickenpox cases are breakthrough cases and this number is likely to grow as a greater percentage of the chickenpox incidence [41,45].

As mentioned above adverse events are relatively uncommon with chickenpox vaccination; however, the increased risk of febrile seizures with MMRV has policy-makers re-considering when they give the first dose of varicella vaccination and whether they continue to provide MMRV to children 12 months old. Furthermore, due to the close relationship between chickenpox and shingles, researchers and policy-makers have also raised concerns about the indirect negative consequences of universal chickenpox vaccination. Multiple modelling studies of the biological and epidemiological relationship between chickenpox and shingles predict that if exogenous boosting exists then the implementation of the chickenpox vaccine, and therefore the reduction in natural boosting opportunities, could lead to an increase in shingles cases [12]. However, the impact of chickenpox vaccination on shingles is unconfirmed, with studies of the burden of shingles post chickenpox vaccination remaining inconsistent [12].

3.5. Infectious disease modelling

3.5.1. General background on infectious disease models

Models are simplified representations of reality, providing a formal framework for analysis by synthesizing information from multiple sources. Models are becoming increasingly useful in health and have been applied to a variety of health conditions, programs and processes. One area of growing interest is using models to represent the spread, prevention and treatment of infectious diseases. Infectious diseases are typified by the fact that the disease survives and is transmitted by travelling from one host to another. This means an individual's risk of getting the disease is dependent on population factors, particularly the number of protected, infected and susceptible people in a population. The fact risk can vary over time depending on disease transmission makes modelling infectious diseases complex. However, disease models can be the only way to predict and measure the consequences and outcomes associated with the prevention and treatment of infectious disease.

Models can be used in the understanding, testing and evaluation of infectious diseases and their prevention and treatment programs. Examples of where infectious disease models have been used include, the calculation of unknown infectious disease parameters (e.g. basic reproductive number), measuring the effectiveness of an intervention, determining population

level effects (e.g. herd immunity threshold), and conducting economic evaluations [46]. One of the big questions that models can help to answer is whether different prevention programs, for example vaccination, are effective at preventing negative disease outcomes. Typically, the only way to measure the effect of a vaccine on incident cases, prior to its implementation, or prior to changing vaccination program (e.g. type of vaccine, schedule, target population), is to use dynamic infectious disease models.

3.5.2. Types of infectious disease models

In recent years there has been an explosion in the types of models used for infectious disease and the choice of model is highly dependent on the research question. A common distinguishing feature of models is whether they are static versus dynamic. Static models have a constant risk and therefore cannot account for the fact that the force of infection may change over time. While static models can capture the direct impacts of vaccination programs (e.g. the number of people who are directly protected through vaccination), they cannot capture the indirect effects (e.g. the number of people protected through vaccination due to a reduction in disease transmission). To capture these indirect consequences, researchers need to use dynamic models. While not always necessary in the estimation of vaccine cost-effectiveness, dynamic models allow the force of infection to change over time. Therefore, the model can explicitly illustrate the spread of infection through populations and with that the indirect effects associated with prevention methods (e.g. vaccination) and treatments (e.g. anti-retroviral for HIV). Examples of indirect effects of vaccination that can be captured by dynamic models include, type- or strain-replacement, immunity boosting effects, herd immunity and shifting of age patterns.

Another key distinguishing factor between models is whether the unit of analysis is the population or the individuals. In an aggregate model, the population is structured into groups (e.g. susceptible, recovered, infected), and transitions between groups occurs based on certain probabilities (e.g. risk of infection). In comparison, in individual-based models there is a system of interacting individuals (e.g. agents). Each agent is defined based on several characteristics (e.g. age, sex, disease status) and population outcomes are emergent from the interaction between individuals. Other model benefits include the memory associated with the model (i.e. can the model consider what has happened to an individual and/or population before), whether it includes a network (i.e. do diseases and messages spread through the contact between

individuals, where connections are based on certain rules, for instance, based on distance or age), and its stochastics (i.e. random events and chance are built into the model, so every model run will be different). Therefore, ABMs may be used when an individual's history of disease and treatment should determine their risk of a certain outcome, for example the very complex medical history of a diabetes patient may provide evidence of their risk of coronary artery disease. Individual-based models are also particularly useful when contact networks can have a profound impact on disease outcomes. For instance, individual-based model may be better suited to represent the spread of sexually transmitted infections, where an individual's connection determines their risk of infection, or measles, where vaccine refusers may congregate in one geographical location.

One of the newest types of models are agent-based models (ABMs), which include one or more populations composed of individual agents. In ABM, each agent is associated with, one or more states (e.g. age state, health or vaccination state), a variety of parameters (e.g. gender,) and have rules for interacting with other agents. These elements of ABM are found in the Person-class of the modelling software Anylogic®. Each agent is embedded in an environment, called Main-class, where they may be part of a contact network connecting individual agents and where messages and disease can pass through the network. ABMs are generally individual-and network-based, dynamic, non-memoryless, and stochastic models. These factors mean ABMs are generally very flexible and can represent complex disease processes, as described above; however, they can be difficult and time-consuming to build and run, and require specific and difficult to acquire data and longer run times.

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CHAPTER 4- EVALUATION OF THE EFFECT OF CHICKENPOX VACCINATION ON SHINGLES EPIDEMIOLOGY USING AGENT-BASED MODELLING

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Rafferty E, McDonald W, Qian W, Osgood ND, Doroshenko A. (2018). Evaluation of the effect of chickenpox vaccination on shingles epidemiology using agent-based modelling. *PeerJ*. Accepted May 30th, 2018. My contributions to this manuscript included conceptualizing the model, conceiving and designing the study, running the experiments, analysing and interpreting the findings and manuscript preparation. Wade McDonald, with the help and guidance of Weichang Qian, updated my original chickenpox agent-based model to run on a larger population, included a more complex distance-based network, represented contacts based on age, calibrated the model to data from the literature, outputted results from each model run, created a system to run the model on multiple computers at one time and oversaw the running of our model experiments. Dr. Nathaniel Osgood, aided in the conception and the design the study, and oversaw all model adaptations and model runs. Dr. Alexander Doroshenko aided in the conception and design of the study and also contributed to the analysis of our findings. All authors helped in the interpretation of findings and in reviewing and editing the manuscript.

In this chapter, we describe the agent-based model we built to represent VZV disease, transmission, vaccination states and coverage, waning and boosting of immunity. We use this model to investigate how chickenpox vaccination in Alberta impacts the incidence and age-distribution of shingles over 75 years post-vaccination taking into consideration a variety of plausible theories of waning and boosting of VZV immunity. We undertook this analysis based on the gaps in the literature identified in **Chapters 2** and **3**, specifically the lack of evidence of the impact of chickenpox vaccination on shingles disease outcomes. Previous models and epidemiological studies on the boosting of VZV-immunity for shingles found that while there is evidence that boosting of VZV exists, there is little evidence for the strength or duration of that boosting effect. Unknowns surrounding the unintended outcomes of chickenpox vaccination has prompted many countries to delay vaccine implementation, even though there is a safe and effective vaccine available. The model described in detail in this chapter also provides the foundation for testing the effectiveness and cost-effectiveness of chickenpox vaccination overall, and for two specific chickenpox vaccine schedules, as described in **Chapters 5** and **6**.

4.1. Introduction

Varicella (chickenpox) and herpes zoster (shingles) are two diseases caused by the varicella zoster virus (VZV). Individuals are generally infected with chickenpox in childhood. In Canada prior to vaccination, approximately 11.7 per 1,000 persons were infected with chickenpox each year, which was estimated to cost about 122 million CAD$ annually [1]. Following primary chickenpox infection, the VZV migrates to the sensory nerve ganglia, where it remains latent and can subsequently reactivate as shingles, which causes a dermatomal rash often accompanied by itching and pain [2]. Shingles was estimated to occur at a rate of 1.2-3.4 per 1000 per year (3.9-11.8 cases per 1,000 per year in those >65 years) in Canada before chickenpox and shingles vaccination [3]. Some studies suggest that the incidence of shingles was increasing in the decades before the introduction of chickenpox vaccination [4–6].

Although much remains unknown about shingles and the reactivation process, research has demonstrated that the maintenance of latency is largely governed by VZV cell-mediated immunity (VZV-CMI). Successful reactivation of shingles occurs when VZV-CMI weakens to a yet unknown level, which is often a result of the normal ageing process [7]. However, the literature shows there are likely other risk factors that can result in inadequate immune response to VZV reactivation at any age, including mental health, stress, comorbid infections (e.g., cytomegalovirus [CMV] infection) and immunosuppressive therapy, and disease-related immunosuppression (e.g. HIV-AIDS) [7]. In parallel to the natural waning of VZV-CMI immunity, one theory posits that exogenous boosting of VZV-CMI can reduce one's risk of shingles reactivation [8–10]. Exogenous boosting occurs when a VZV immune individual is exposed to a case of chickenpox or shingles.

The theory of exogenous VZV-CMI boosting has sparked a debate about whether the chickenpox vaccine will limit the boosting of immunity to shingles and therefore increase the incidence of the disease; however, the empirical data to-date is largely inconclusive [4,11]. This debate has prompted many countries, including the United Kingdom and France, to delay the implementation of a universal chickenpox vaccine, even though there is a safe and effective chickenpox vaccine available [12]. In comparison, other countries, including Canada and the USA, currently recommend a two-dose chickenpox vaccination schedule [13]. Alberta introduced a universal one-dose chickenpox vaccination program for 12-month-olds in 2001 and in 2012 added a second dose for children aged 4-6 years. Russell *et al.* found that shingles

incidence was increasing in Alberta in the period 1994-2010, both before and after the introduction of the chickenpox vaccination [4].

The unique connection between chickenpox and shingles makes independently exploring their disease dynamics difficult. Using mathematical modelling to study the interacting factors related to these diseases – in particular, how chickenpox vaccination may impact shingles disease and epidemiology – complements conventional epidemiological studies and offers a unique approach to evaluating effects of vaccination in a controlled study using simulated data.

Most previous modelling studies of shingles and chickenpox have been conducted using aggregate population-level models [6]. Both agent-based and aggregate models can simulate the indirect effects of varicella vaccination, including the changing risk of disease over time, herd immunity, age-category specific mixing and rates, and increasing age of infection. However, agent-based models (ABMs) provide a number of advantages in the study of many infectious diseases, including allowing the exploration and measurement of disease dynamics at multiple levels and the adjustment of both individual and population parameters [14–18]. In the study of the VZV, ABMs can provide for realistic and comprehensive simulation of the transmission of infection and boosting of immunity by explicit modelling of network-mediated contacts, and flexibility in specifying interpersonal contact. ABMs allow the simulation of between-host dynamics (e.g., transmission) at an individual level, while also capturing spatial limits on such transmission and allowing the simulation of continuous within-host dynamics, including for both aging and individual waning of VZV-CMI; the characterization of such factors as continuous processes offers flexibility in terms of reporting and characterization individual-level dynamics [15–17,19].

ABMs can further represent detailed elements of vaccination, including vaccine attitudes, uncertainties in vaccine coverage and – critically for this study – continuous waning of vaccine immunity. Importantly for supporting options for later expansions and refinements of this model, the individual-level representation can readily represent reporting and vaccination attitudes dynamics based on family context. As ABMs support reporting an individual's disease or vaccination status in light of their history, catch-up immunization and breakthrough illness can also be represented in a modular manner that scales well to more complex vaccination regimes. Finally, ABMs take into account stochastics and readily accommodate large number of

dimensions of heterogeneity, including sex, age, spatial location, comorbid conditions, and detailed information on condition-specific individual history [16–19].

A systematic review of empirical and modelling studies on the boosting of VZV-CMI for shingles found that while there is evidence that boosting of VZV-CMI exists, there is little evidence of the strength or duration of that boosting effect [6]. The majority of chickenpox vaccination models that incorporated boosting have predicted there will be an increase in shingles incidence post chickenpox vaccination; however, most of them have assumed a high force of boosting [20–22]. While modelling studies have explored the plausibility of various types of boosting (e.g., progressive immunity, partial immunity, temporary immunity) [22,23], there is little exploration of the duration of shingles immunity following boosting and the rate at which an individual's immunity to VZV wanes over time, and how changing assumptions regarding these factors may impact the rate of shingles following chickenpox vaccination.

Within this work, we sought to develop an ABM of chickenpox and shingles disease and vaccination based on current immunological, medical and epidemiological data, and replicate the epidemiology of chickenpox and shingles in Alberta, Canada before chickenpox vaccination using diverse quantitative theories of waning and boosting of VZV immunity. In Alberta, universal chickenpox vaccination has been in place since 2002, and detailed population demographics and chickenpox and shingles epidemiological data is available for both before and after vaccine implementation. The primary objective of this study was to determine how chickenpox vaccination in Alberta impacts the incidence and age-distribution of shingles over the 75-year post-vaccination period, by determining plausible values for waning of natural immunity and the duration of exogenous boosting (i.e. the length of protection following a boosting event).

4.2. Methods

We developed an ABM using the multi-method simulation software AnyLogic® Professional (version 7.3.7), that represents chickenpox transmission, chickenpox and shingles disease and vaccination states, as well as the waning and boosting of VZV immunity **(Data reference 1).** The model is initialized after a 75-year burn-in period, with any calibration or experimentation taking place after that period. We included such a burn-in period representing the average lifespan, to ensure that individuals were at different stages of waning of VZV immunity and therefore at different risk of getting shingles. A long burn-in period meant when

we started running the experiments there were some agents in the recoveredCP state who had had their natural immunity to VZV waned almost to zero (i.e. about to transition to infectedShingles) and other agents who were at the start of the waning process. This study was approved by the Health Ethics Research Board at the University of Alberta, study ID Pro00068334.

4.2.1. Model structure and agent-characteristics

Statecharts related to within-host dynamics of the model are shown in **Figure 4.1A.** A disease statechart where agents are in protected, susceptible or disease states determined an agents' probability of contracting chickenpox or shingles. The chickenpox and shingles vaccination schedules' statecharts represented which vaccination each agent received. The chickenpox vaccination schedule was modelled based on the Alberta VZV vaccination policy [24]. Agents become due for chickenpox vaccines at the ages of 12 months for the first dose and at 4-6 years - for the second dose **(Figure 4.1B.).** A representation of one-dose shingles vaccination given to individuals 50 years or older is depicted in the statechart shown in **Figure 4.1C.** However, currently shingles is not part of the publicly funded schedule in Alberta and therefore was not included as part of this analysis. As our model was calibrated to data from before the shingles vaccine was available in Canada, excluding the shingles vaccine did not impact our ability to accurately calibrate our model. An agent receives a vaccine dose with a probability based on its vaccine attitude as described below. If an agent receives the second dose but has not yet received the first, it may also receive a catch-up of the first dose with a certain probability. These probabilities are specified by parameters, as shown in **Table 4.1.** A full list of the parameters and their values are available in **Appendix C.** A demographic statechart represented Alberta births, ageing and mortality characteristics **(Figure 4.1D)**.

An agent's chance of being infected with chickenpox was dependent on whether they came into contact with someone with infection and the risk of transmission on such a contact. In comparison, an agent's likelihood of getting shingles was determined by their individual waning immunity timer. After chickenpox infection (i.e. when an agent enters the recoveredCP state), a countdown on "Immunity Waning Time" initiates; when it completes, the agents become susceptible to shingles (i.e. transition to infectedShingles at a specified rate). The "Immunity Waning Time" was represented by a formula derived from Ogunjimi et al. [25] and further by calibration **(Figure 4.2 & Table 4.2).** This equation inherits assumptions whereby force of

reactivation is represented by a gamma distribution, initial CMI is represented by a normal distribution and the waning of immunity rate for shingles is a fixed rate that can be altered using a coefficient, specifically the waning of immunity coefficient (WoI) [25]. The WoI is a parameter, whereby we can easily modify the waning of immunity rate by age. Furthermore, to account for the small but sharp increase in childhood shingles cases as observed in Russell et al. [4], we included a small proportion of the population between the ages of 0 and 19 (5%) who had a short waning of immunity timer, allowing the model to account for individuals who may have a weaker force of boosting, lower initial CMI (e.g., immunocompromised) or a very quick waning of the immunity rate.

An agent's "Immunity Waning Time" could also be increased by an exogenous boosting event, which occurred when an agent who is recovered from chickenpox is re-exposed to a case of chickenpox or shingles. Therefore, an agent's chance of getting shingles was also determined by the number of years they were protected through boosting, what we call the duration of immunity through boosting (DoB). The model assumed progressive boosting, as postulated by Guzzeta et al. [22] and therefore the number of years of boosting protection was calculated by multiplying the number of times an agent comes into significant contact with the VZV by the duration in years of each boosting event. The number of boosting events was determined through the distance-based contact network and the duration of each boost was equal to the number of years of added protection from shingles derived through each boost. Altering the quantitative values of DoB and WoI of shingles resulted in significant changes in the incidence of shingles in the population.

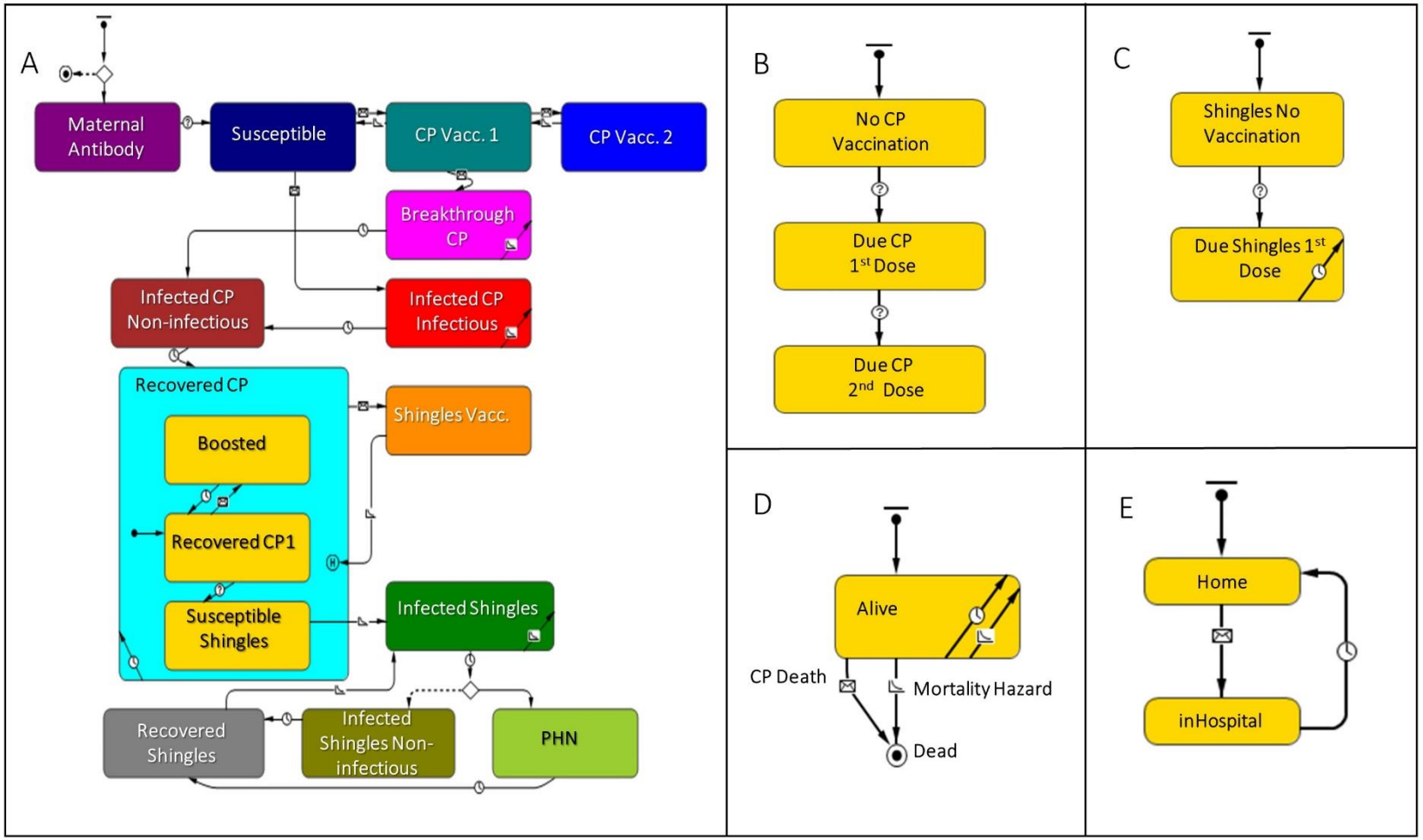

Figure 4.1. Statechart structure for ABM (A) Disease and protection **(B)** Chickenpox vaccination schedule **(C)** Shingles vaccination schedule **(D)** Demographics **(E)** Hospitalization

Table 4.1. Data sources, key parameter values and values of calibration

Parameter category	Parameter Name	Description	Value	Data Source
Demographics	Population size	Population size at the model's initialization.	500,000	
	Mortality rates	Life tables for Alberta age group used to estimate mortality rates in our population	Table- available from Statistics Canada	Statistics Canada [26]
	Fertility rates	Pregnancy outcomes (live birth) for Canada by age group	Table- available from Statistics Canada	Statistics Canada [27]
	Age distribution	Age distribution of the population at the model's initialization	Table- available from Statistics Canada	Statistics Canada [28]
Disease Mechanisms	Waning of immunity time (shingles)	This variable is calculated for each individual when they reach the recoveredCP state and can change with natural exogenous boosting of shingles immunity (i.e. contact with a case of chickenpox and shingles). A full description of how it is calculated is presented in **Figure. 4.2.**	'Years protected through infection' (includes parameters 'initial cell-mediate immunity VZV', 'force of reactivation', waning of immunity rate and coefficient) + 'Years protected through boosting' ('duration of boosting' and number of boosting events)	Ogunjimi et al. [25]
	Initial cell-mediated immunity VZV	The distribution across the population of cell-mediated immunity for shingles derived from initial infection with VZV. (See **Figure 4.2**)	Max (0.001, normal (0.05,1))	Ogunjimi et al. [25]
	Force of reactivation	Represents the distribution of force of reactivation for shingles. It is a unitless value used to calculate the 'waning of immunity time'. (See **Figure 4.2**)	Gamma distribution (2,0.1,0)	Ogunjimi et al. [25]
	Waning of immunity rate shingles	Annual loss of protection based on VZV-CMI.	0.4	Ogunjimi et al. [25]

	Waning of immunity coefficient shingles (WoI)	Coefficient to determine the annual loss of protection based on VZV-CMI. A coefficient allowed us to easily modify the waning of immunity rate with a parameter, specifically by age.	Values tested in calibration: 0.45-0.93 Values included in the analysis: 0.50-0.74 See **Table 4.2**	Calibration
	Duration of exogenous boosting (DoB)	Number of years before your protection returns to previous levels (i.e. extra years protected) following an exogenous boost from a shingles or chickenpox case.	Values tested in calibration: 0.42-10 Values included in the analysis: 2-7 See **Table 4.2**	Calibration
Disease Propagation	Exogenous infection rate (1/Year)	Represents rate per year of chickenpox infection imported from outside the pop.	17.83	Calibration
	Probability of chickenpox infection on contact	Determines the likelihood that chickenpox will be transmitted when an agent (with normal or breakthrough chickenpox, or shingles) contacts a susceptible.	Normal: 0.781 Breakthrough: 0.234 Shingles: 0.234	Ceyhan et al. [29] Gershon et al. [30] Calibration
Network characteristics	Connection Range (Length)	Distance of an individual's connection range. The range depended on whether you were included in the preferential mixing age or the normal mixing age.	Preferential Range= 21.245 Normal Range= 8.958	Control mixing patterns were calibrated based on cumulative incidence and age-distribution of chickenpox and shingles over time. Statistics Canada [26–28] Mossong et al. [31]
	Shingles connection range modifier	A ratio to lower the connection range of individuals with HZ to make it less infectious than chickenpox.	0.124	
	Base contact rate (1/Day)	Number of contacts per agent per day, which dependent on if you were part of the preferential or normal age range.	Preferential contact rate= 20; Normal contact rate= 3	
	Preferential mixing age (Year)	Age group where we have increase the connection range and base contact rate to better reflect the dynamics in the population.	1-9 years	

	Population density (Agents per length)	Represents the number of agents per arbitrary distance for urban and rural population. This parameter in combination with connection range determines the number of connections an agent has in our model.	Urban: 0.3 Rural: 0.2	
Chickenpox vaccine parameters	Vaccination attitude in the population (%)	Distribution of vaccine rejector, hesitant and acceptors in the population.	Acceptor = 65, Hesitant = 30, Rejector = 5	Vaccine coverage generated by the model through calibration
	Probability Catch-Up (%)	Probability that an individual will get a catch-up vaccine when due for second dose vaccination.	55	
	Probability first dose vaccination (%)	Probability an individual will get first dose vaccination given their vaccine attitude.	Acceptor= 97, Hesitator= 75, Rejector= 3	Alberta Health [32]
	Probability second dose vaccination (%)	Probability an individual will get second dose vaccination given their vaccine attitude.	Acceptor= 98, Hesitator= 82, Rejector= 33	
	Primary vaccine failure chickenpox (%)	The percent of individual that do not have an immune response to chickenpox vaccination.	1st dose= 16-24 2nd dose= 5-16	Gershon et al. [30] Bonanni et al. [33] Duncan et al. [34]
	Waning of chickenpox vaccine immunity (1/Year)	The rate that chickenpox vaccine immunity wanes each year.	1st dose protected= 0.02 2nd dose protected= 0.00	Gershon et al. [30]

Shingles Immunity Waning Timer = (1) Years Protected Through Infection + (2) Years Protected Through Boosting

(1) Years Protected Through Infection = $\frac{\min(0,\log(\text{forceOfReactivation}/\text{InitialCMI})}{\min(0,\log(1-\text{waningOfImmunityRateShingles})}$

(2) Years Protected Through Boosting= Number of times an agent comes into significant contact with VZV (in the form of chickenpox or shingles) X The duration in years of each boosting event

Where:

ForceOfReactivation= The strength of shingles reactivation, i.e. the amount of VZV-CMI need to stop reactivation in the form of shingles, the value for each individual in our population is drawn from a gamma distribution.

InitialCMI= The initial level of VZV-CMI protection conferred following chickenpox, the value for each individual in our population is drawn from a normal distribution.

WaningOfImmunityRateShingles= the rate of annual loss of VZV protection (1/years). The WaningOfImmunityRateShingles is a fixed rate that can be altered in our model using the waning of immunity coefficient.

Duration of each boosting event= The number of years of protection gained through each significant boosting event, this value is based on calibration results.

This equation was derived from the model presented in Ogunjimi et al. [25]

Figure 4.2. Equations to calculate the shingles immunity waning timer

Table 4.2. Calibration results to determine duration of immunity following boosting and waning of immunity coefficient

	Duration of immunity following boosting- DoB (years)	Waning of immunity coefficient- WoI (1/year)	P-values[1]
Combination 1[2]	0.42	0.45	<0.001
Combination 2	2	0.50	0.051
Combination 3	3	0.55	0.313
Combination 4	4	0.60	0.052
Combination 5 (Baseline Scenario)[3]	5	0.63	Reference
Combination 6	6	0.68	0.963
Combination 7	7	0.74	0.121
Combination 8	8	0.79	0.001
Combination 9	9	0.85	<0.001
Combination 10	10	0.93	<0.001

[1]P-values for Mann-Whitney U test comparing age-specific shingles incidence sum of residuals squared for Combination 5 (Baseline Scenario, DoB=5 years WoI= 0.63) to all other Combinations (1-4 and 6-10). Calibrations scenarios deemed statistically not different (i.e., p-value >0.05) were included in the main experiment. Calibration scenarios which were statistically different from the best-fit calibration experiment were excluded.
[2]Represents combinations of DoB and WoI, all other parameters in the model stayed the same.
[3]Baseline scenario was the combination of DoB and WoI with the smallest absolute median difference between model incidence rates of shingles and empirical data for each age group as determined by lowest sum of residuals squared

4.2.2. Contacts, network and spatial context

The VZV model represented agents in a stylized geographic area, where agents are connected to other agents based on their proximity to one another (a distance-based network). When agents are randomly placed in the model environment they are connected to all other agents within their connection range (*connectionRange_Norm*). The contact rate (*baseContactRate_Norm*) determines the number of contacts (e.g. messages) an agent makes to a connected agent per day. It is through these messages, sent through connections and contacts, that individuals can transmit chickenpox infection and provide boosting of VZV. These contact and mixing patterns were calibrated to cumulative incidence and age-distribution of chickenpox over time using a pattern-oriented modelling approach [4,35,36]. Moreover, to capture the transmissibility of VZV, we included a parameter for the risk of chickenpox infection on contact. We included different infection rates for when a susceptible agent came into contact with a normal chickenpox case (*probCPDiseaseOnContact*), a breakthrough case of chickenpox (*probCPDiseaseOnContactWithBreakthrough*) and a shingles infection

(*probCPDiseaseOnContactWithShingles*) [29]. These probabilities also determined the likelihood of someone receiving a boost of VZV immunity from each infection type.

Furthermore, to represent the increased contact time and range of connectivity among day-care and early school-aged children, we incorporated differing connection ranges and contact rates based on age [31]. Those aged one to nine years were considered 'preferential contacts' in our model, and therefore have a higher contact rate (*baseContactRate_Pref*) and connection range (*connectionRange_Pref*) when interacting with individuals within the same age range. We chose this group to represent 'Preferential Contacts' as these are the age groups with the highest rates of chickenpox infection as described by Kwong et al. [35]. These network adjustments ensured more realistic contact network assumptions than random-mixing and compartmental models do, such that not only age-group preferences of contacts were captured, but also increased global connectivity due to bridging effects of younger age groups was considered (**Data reference 2**). We also included a low-density periphery and a higher density central region to better represent how disease spreads in a typical public health district in Albert (or comparable jurisdiction) spanning an urban center and rural regions. Approximately 20% of our population were part of low density regions and the remainder, 80%, reside in a high-density region.

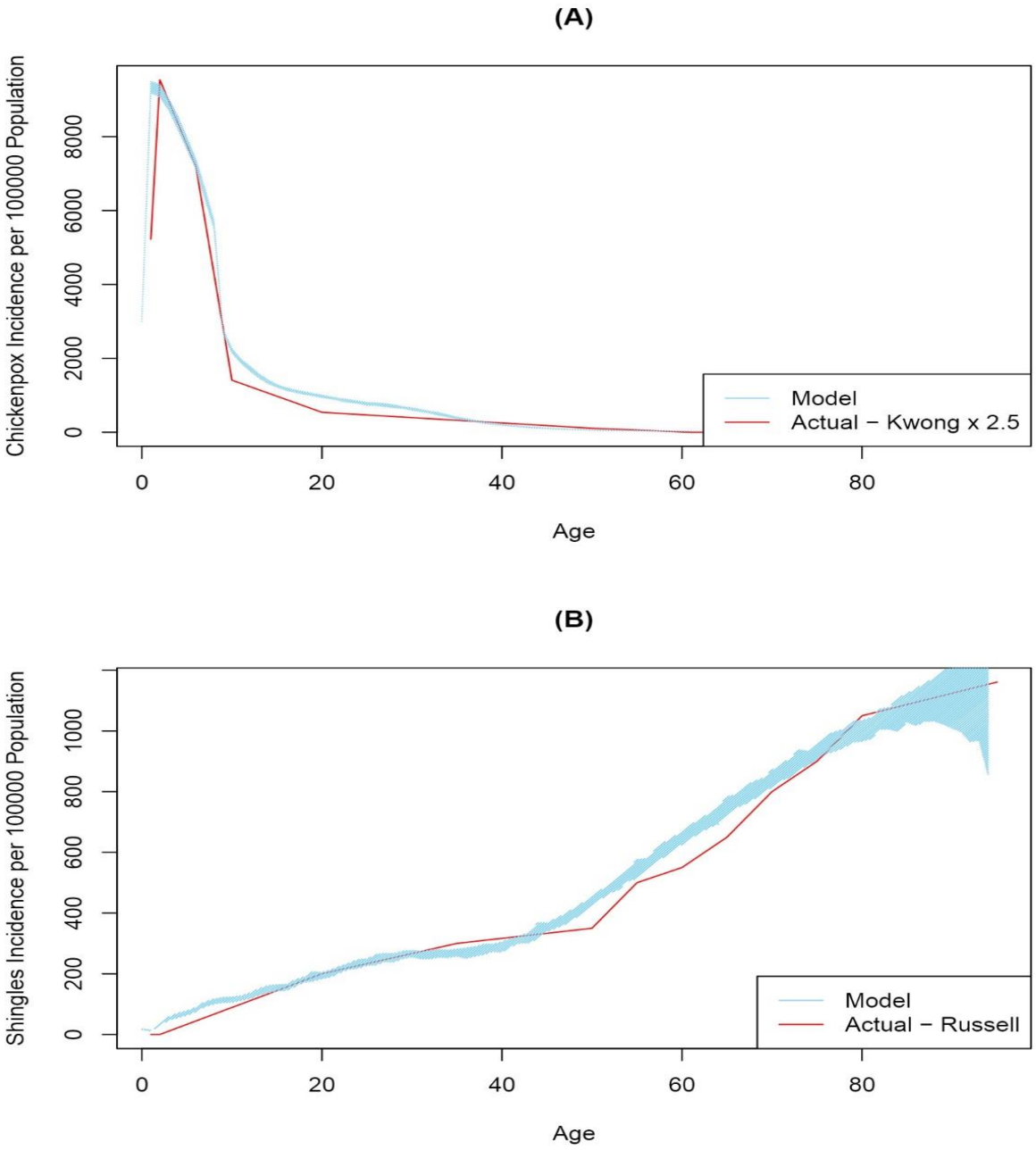

Figure 4.3. Model-generated (blue line) and published (red line) age-specific incidence rates for chickenpox and shingles used in model calibration – baseline scenario (A) Model data is based on 30 paired simulations for the baseline scenario (DoB= 5 years; WoI= 0.63); empirical data as described by Kwong et al. [35]; best fit is achieved at 2.5 multiple of empirical data; **(B)** Model data is based on 30 paired simulations for the baseline scenario; empirical data as described by Russell et al. [4] (In all images the blue polygon represents pointwise minimum and maximum values)

4.2.3. Parameterization

To parameterize the model, we conducted a comprehensive literature review of chickenpox and shingles disease, including modelling, epidemiological, and immunology studies and drew evidence from Alberta's Interactive Health Data Application (IHDA) [37]. The main parameters are listed in **Table 4.1.** We drew demographic data, including Alberta life tables, and population and age distributions, and Canadian fertility rates from Statistics Canada [26–28]. Chickenpox vaccination parameters, such as those associated with primary vaccine failure and waning of vaccination immunity were derived from literature [30,33,34]. We built the mechanism whereby vaccine coverage was generated by our model based on distribution of vaccination probabilities and population vaccination attitudes as described by Doroshenko et al. [38]. We classified all individuals into three groups: those who accept, reject and are hesitant to receive vaccination, and we assigned vaccination probabilities for each of these groups. We used calibration to ensure that model-generated vaccine coverage rates were comparable to those reported in Alberta [37]. For the baseline scenario in the main experiment, chickenpox vaccination maintained an average coverage for the first dose of 85.58% (95% CI 85.54-85.62) and second dose coverage of 80.28% (95% CI 80.24-80.32) across all years and all model runs.

4.2.4. Calibration and validation of the model

We calibrated our model using a step-wise approach. First, we ran an initial AnyLogic® calibration experiment to determine the values for four unknown parameters in our model, duration of immunity following exogenous boosting (DoB), waning of immunity coefficient (WoI) (the parameter that modified the waning of immunity rate), exogenous infection rate (i.e. the number of chickenpox cases brought in from outside the simulated population) and shingles connection range (i.e. modification factor for the connectionRange for people with shingles, to account for the closer contact required to spread VZV through shingles in comparison to chickenpox). The calibration experiment automatically varied these parameters and validated model output against age-specific incidence of shingles prior to vaccination as described by Russell et al. [4] **(Figure 4.3B)** and chickenpox prior to vaccination, as described in Kwong et al. [35] **(Figure 4.3A).** As we only had empirical data for medically-attended chickenpox [35], we tested different underreporting factors and found that reported chickenpox cases constituted approximately 40% of all cases in our model (an underreporting factor of 2.5, consistent with previous studies that suggest the degree of underreporting can range between 2.5 and 7.7 in a country where chickenpox is notifiable) [39]. Furthermore, the overall chickenpox incidence

when the vaccination function was disabled in the model was consistent with findings in Canada prior to vaccination [40].

This initial calibration experiment predicted an exogenous infection rate of 17.8 per year and a shingle connection range modifier of 0.12 (suggesting shingles is 8 times less likely to spread VZV infection than chickenpox). Furthermore, based on the automated experiment values for DoB of 0.42 years and a waning of immunity coefficient of 0.45/year we produced age-specific incidence rates for shingles and chickenpox consistent with empirical data.
Using the initial calibration values described above as a starting point, we then further investigated whether different combinations of DoB and WoI could reproduce empirical data. We used a pattern-oriented modelling approach [36] to compare the incident rates resulting from a range of plausible values for DoB and WoI to the empirical incidence rates for chickenpox and shingles [4,35,36,41,42]. At this stage we considered paired values of DoB and WoI to have satisfied calibration if the resulting overall rate of chickenpox and shingles, over a model run of 100 years on 50,000 population, was within 10% of the empirical values [36,41,42]. Based on these guidelines we found nine other values for a combination of DoB and WoI that met the second step of calibration.

Finally, we then ran the ten combinations that met the initial calibration criteria noted above for a period of 100 years on 500,000 population sample. Output from each run was then compared to empirical data on age-specific incidence rates for chickenpox and shingles. We calculated the absolute median difference between model incidence rates of shingles and empirical data for each age group to determine which combination had the smallest difference as determined by lowest sum of residuals squared. The combination with the lowest sum of residuals squared (27.95) for shingles was then considered our baseline scenario in our main experiment, which represented best fit (Baseline scenario= DoB 5 years and WoI 0.63) **(Data reference 3).** The sum of residuals squared from each combination was then compared to the baseline scenario and tested for statistically significant difference using the Mann-Whitney U test at the 5% level of significance. Based on the findings of the statistical tests and as a form of scenario analysis, we included both the baseline scenario along with any other DoB and WoI combinations that were not statistically different (p value >0.05) from baseline. These model runs became the scenarios in our main experiment.

4.2.5. Main experiment

For each of the six scenarios chosen for the main experiment, we conducted at least 30 paired runs, with and without chickenpox vaccination. Running paired runs for each scenario allowed the measurement of differences in shingles rates with and without vaccination for each DoB and WoI combination. Paired model runs were given the same random seed to ensure consistency between parameter and variables in each of the pairs. To determine the number of model runs required to achieve saturation of the results we compared the distributions of the chickenpox and shingles incidence from two sets of 15 model runs. We found no significant difference in distribution for chickenpox and shingles incidence using the Kolmogorov-Smirnov Two Sample Test (see **Appendix E, Tables E-1 and E-2**). Based on these findings we ensured each scenario was run at least 30 times, to support the ability of our results to predict a range of results with accuracy. Chickenpox vaccination was represented as part of a two-dose schedule, as described above. In our model, we implemented chickenpox vaccination starting at 25 years after the initialization of the model and continued for 75 years. We calculated 95% predictive intervals (2.5^{th} and 97.5^{th} percentiles) for change in cumulative shingles incidence between vaccination and no-vaccination scenarios for each time points and scenario. The cumulative incidence rate of shingles cases between the runs with and without chickenpox vaccination were compared at the 5% level of significance using the Kolmogorov-Smirnov statistical test at four different time periods, specifically at 10, 25, 50 and 75 years, following introduction of vaccination.

4.2.6. Sensitivity analysis

We ran several scenario analyses that tested how varying vaccination parameters may impact the count of shingles cases following chickenpox vaccination. Specifically, we compared a one-dose to a two-dose chickenpox vaccine schedule. In a separate set of analyses, we compared coverage rates by moving 10% of hesitant individuals to vaccine acceptors (higher vaccine coverage) in one sensitivity analysis and 10% of hesitant individuals to vaccine rejectors (lower vaccine coverage) in the second sensitivity analysis. Furthermore, we tested the impact of removing the boosting of shingles immunity (i.e., positing no added years of protection on contact with a chickenpox/shingles case) to see the overall impact of removing this biological effect on the shingles incidence estimates both before and after chickenpox vaccination. We calculated 95% predictive intervals for change in cumulative shingles incidence between vaccination/no-vaccination scenarios for each time point and sensitivity analysis combination.

4.3. Results

4.3.1. Input calibration

Based on the last step of our calibration we found that the age-specific shingles residuals for the baseline scenario (DoB= 5 years; WoI= 0.63) were not significantly different to five of the other combinations **(Table 4.2).** These combinations were then included as six scenarios in our main experiment (Scenario 2-7, sum of residuals squared for shingles ranges from 27.95 to 41.51, p-value >0.05) **(Date Reference 2)**. All sum of residuals squared for chickenpox by age group were not statistically different from baseline for each combination of DoB and WoI (sum of residuals squared for chickenpox ranges from range 249.20 to 251.00, p-value >0.05). As one of the calibration validity tests, we tried to fit model to empirical data with no boosting, however when we disabled boosting we could not replicate the age-specific incidence rate observed in Alberta prior to vaccination [4].

4.3.2. Main experiment

Chickenpox vaccination lead to a large drop in chickenpox cases across all six scenarios. In the baseline scenario, the cumulative incidence of chickenpox dropped from 1,254 cases per 100,000 person-years pre-chickenpox-vaccination to 193 cases per 100,000 person-years 10 years after the vaccine implementation. The cumulative incidence of chickenpox was further reduced to 49 cases per 100,000 person-years 75 years following vaccination. In comparison, all scenarios from 10-years and 25-years post-vaccination showed significantly greater shingles incidence with vaccination compared to the no- vaccination **(Table 4.3).** However, the degree of this increase and its subsequent decline was markedly different between experiments **(Figure 4.4 and Table 4.3).** For instance, in Scenario 2 there was an increase of approximately 22.73 cases per 100,000 person-years after 10 years; by comparison, in Scenario 7 the magnitude of the increase was greater at 99.29 cases per 100,000 person-years over that decade ($p < 0.001$). At 75 years post-vaccination, cumulative incidence ranged from a decline of 69.55 to an increase of 71.21 per 100,000 person-years for 2 and 7 years of boosting respectively ($p < 0.001$). By the 75-year interval, the shingles incidence in all experiments was below the rate with no-vaccination **(Figure 4.4)**; however, the cumulative incidence in Scenarios 5-7 was still higher with vaccination than without. In all our scenarios, vaccination did eventually lower the overall rate of shingles; however, the amount of time was dependent on the DoB and the WoI.

Table 4.3. Change in all-ages cumulative incidence of shingles over 75 years after implementation of chickenpox vaccination, by scenario and time period.

	Time periods							
	T0-T10		**T0-T25**		**T0-T50**		**T0-T75**	
Scenario number	**Cumulative incidence-chickenpox vaccination scenario[1]**	**Change in cumulative incidence[2,3] (95% CI)[4] *[% change]***	**Cumulative incidence-chickenpox vaccination scenario**	**Change in cumulative incidence (95% CI) *[% change]***	**Cumulative incidence-chickenpox vaccination scenario**	**Change in cumulative incidence (95% CI) *[% change]***	**Cumulative incidence-chickenpox vaccination scenario**	**Change in cumulative incidence (95% CI) *[% change]***
Scenario 2 (DoB=2yr; WoI= 0.50)	405.61	22.73 (18.78, 25.18) *[5.4%]*	402.86	18.55 (15.77, 20.23) *[4.8%]*	375.10	-8.66 (-11.10, -5.94) *[-2.3%]*	313.35	-69.55 (-72.13, -66.90) *[-18.2%]*
Scenario 3 (DoB=3 yr; WoI= 0.55)	453.01	41.08 (35,78, 45,18) *[10.0%]*	461.13	47.97 (45.68, 50.70) *[11.6%]*	436.68	23.90 (21.59, 26.25) *[5.8%]*	365.29	-48.317 (-51.84, -46.05) *[-11.7%]*
Scenario 4 (DoB=4 yr; WoI= 0.60)	492.83	59.0993 (56.14, 64.78) *[13.7%]*	515.82	82.20 (79.16, 85.14) *[18.9%]*	497.10	61.59 (58.03, 64.78) *[14.1%]*	413.98	-22.36 (-26.94, -18.47) *[-5.1%]*
Baseline Scenario (DoB=5 yr; WoI= 0.63)	491.18	71.74 (64.84, 76.68) *[17.1%]*	530.23	109.54 (105.29, 112.95) *[26.0%]*	520.23	97.40 (93.73, 100.75) *[23.0%]*	434.60	10.31 (4.6, 13.73) *[2.4%]*
Scenario 6 (DoB=6 yr; WoI= 0.68)	512.58	84.05 (75.58, 101.22) *[19.7%]*	573.94	144.39 (139.34, 153.38) *[33.6%]*	572.35	138.55 (133.31, 146.45) *[31.9%]*	475.83	39.79 (34.35, 46.30) *[9.1%]*
Scenario 7 (DoB=7 yr; WoI= 0.74)	537.47	99.29 (90.42, 108.96) *[22.7%]*	627.23	185.68 (177.69, 190.64) *[41.9%]*	632.65	185.49 (181.76, 190.64) *[41.5%]*	522.70	71.21 (67.05, 76.41) *[15.8%]*

[1]Median shingles cumulative incidence with chickenpox vaccination per 100,000 person-years (averaged over 30 or more model runs).
[2]Change in shingles cumulative incidence per 100,000 person-years calculated as the median shingles incidence with chickenpox vaccination minus the median shingles incidence without chickenpox vaccination. Positive number represents an increase in cumulative incidence and negative number – a decrease.
[3]Using the Kolmogorov-Smirnov test all changes in cumulative incidence for every time and scenario combination were statistically significant ($p<0.05$).
[4]95% predictive interval (2.5^{th} and 97.5^{th} percentile)

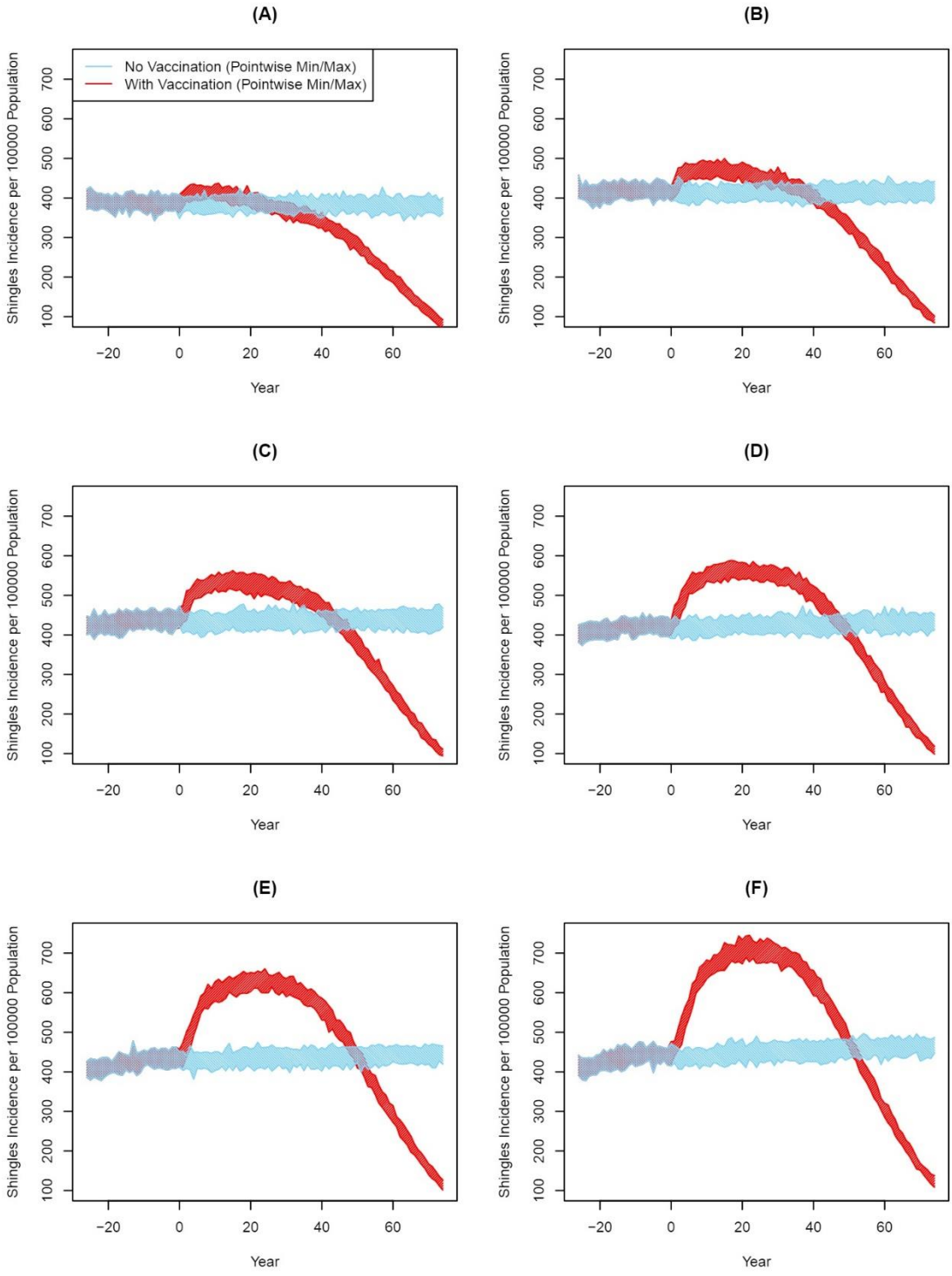

Figure 4.4. All-ages shingles annual incidence over time after implementing chickenpox vaccination by duration of immunity following boosting, 30 paired simulations (A) Scenario 2 (DoB= 2) **(B)** Scenario 3 (DoB=3) **(C)** Scenario 4 (DoB=4) **(D)** Scenario 5 (DoB=5) **(E)** Scenario 6 (DoB=6) **(F)** Scenario 7 (DoB=7) (In all images the blue polygon represents pointwise minimum and maximum values)

At the 10-year interval post-vaccination, all age groups greater than 10 years old showed small but equal increases in the number of shingles cases. However, at each subsequent time point (as a greater number of persons of younger age are protected with chickenpox vaccination from initial infection with the virus), cases of shingles were progressively more concentrated in the older age-groups. In contrast, in the younger age group we observed a decrease in shingles almost immediately following chickenpox vaccination **(Figure 4.5)**.

We also noted an interesting phenomenon in the no-vaccination model runs. There was an overall increase in shingles cases even without vaccination; in the baseline scenario, 97% of model runs found the incidence of shingles was lower at time 10 years (median- 418 per 100,000 person-years), in comparison to time 75 years (median- 425 per 100,000 person-year). The age-structure of the population was also changing over this time period (i.e. skewed to an older population), which may account for this increase in shingles incidence over time. Moreover, the average number of boosts per individual calculated in our model over their life-time (with no chickenpox vaccination) was 1.83 with the majority of people receiving 0 or 1 boosts.

4.3.3. Sensitivity analysis

The only sensitivity analysis where shingles incidence was significantly different from baseline was when we removed exogenous boosting from the model (**Table 4.4**). In fact, removing the biological effect of boosting had a substantial impact on the number of shingles cases both before and after vaccination, with cases rising to levels much higher than what was seen in Alberta prior to vaccination [4]. Without chickenpox vaccination, the shingles rate was very high at 724 cases per 100,000 person-years. Simultaneously, this is the one analysis where the rates begin to decline immediately following vaccination with a decline in cumulative incidence of 215 per 100,000 person-years 75 years after the implementation of the chickenpox vaccine **(Table 4.4).** The 95% predictive intervals for the change in shingles incidence for all other sensitivity analyses at all other timepoints overlapped dramatically with the change in shingles incidence for the baseline scenario.

Table 4.4 Scenario analysis - change in all-ages cumulative incidence of shingles over 75 years after implementation of chickenpox vaccination, by scenario and time period

	Time periods							
	T0-T10		**T0-T25**		**T0-T50**		**T0-T75**	
Sensitivity analysis number	**Cumulative incidence-chickenpox vaccination scenario[1]**	**Change in cumulative incidence[2] (95% CI)[3]** *[% change]*[4]	**Cumulative incidence-chickenpox vaccination scenario[1]**	**Change in cumulative incidence (95% CI)** *[% change]*	**Cumulative incidence-chickenpox vaccination scenario**	**Change in cumulative incidence (95% CI)** *[% change]*	**Cumulative incidence-chickenpox vaccination scenario**	**Change in cumulative incidence (95% CI)** *[% change]*
Baseline scenario (DoB=5 yr; WoI= 0.63)	491.18	71.74 (64.84, 76.68) *[17.1%]*	530.23	109.54 (105.29, 112.95) *[26.0%]*	520.23	97.40 (93.73, 100.75) *[23.0%]*	434.60	10.31 (4.6, 3.73) *[2.4%]*
One dose vaccination schedule	489.67	70.94 (64.74, 75.89) *[17.0%]*	527.84	107.12 (102.41, 110.93) *[25.4%]*	514.33	91.39 (86.71, 94.54) *[21.6%]*	435.07	10.20 (5.07, 13.92) *[2.4%]*
Lower coverage rates	489.09	70.026 (62.66, 76.22) *[17.0%]*	528,87	108.37 (104.45, 112.21) *[25.7%]*	519.25	96.15 (92.74, 99.07) *[22.7%]*	434.84	10.00 (5.09, 12.64) *[2.3%]*
Higher coverage rates	490.31	72.15 (62.91, 78.94) *[17.2%]*	530.73	109.62 (104.88, 114.77) *[26.0%]*	520.88	97.38 (94.41, 102.03) *[23.0%]*	434.	9.65 (4.84, 14.17) *[2.3%]*
Removing exogenous boosting	725.12	-8.76 (-11.88, -6.50) *[-1.2%]*	702.40	-30.64 (-33.46, -28.38) *[-4.2%]*	632.66	-97.97 (-102.63, -94.51) *[-13.4%]*	512.40	-215.64 (-220.93, -210.84) *[-29.6%]*

[1]Median shingles cumulative incidence with chickenpox vaccination per 100,000 person-years (averaged over 30 or more model runs).
[2]Change in shingles cumulative incidence per 100,000 person-years calculated as the median shingles incidence with chickenpox vaccination minus the median shingles incidence without chickenpox vaccination. Positive number represents an increase in cumulative incidence and negative number – a decrease.
[3]95% predictive interval (2.5th percentile and 97.5th percentile)
[4]Percent change was calculated as the number with vaccination minus the number without vaccination divided by the number with vaccination

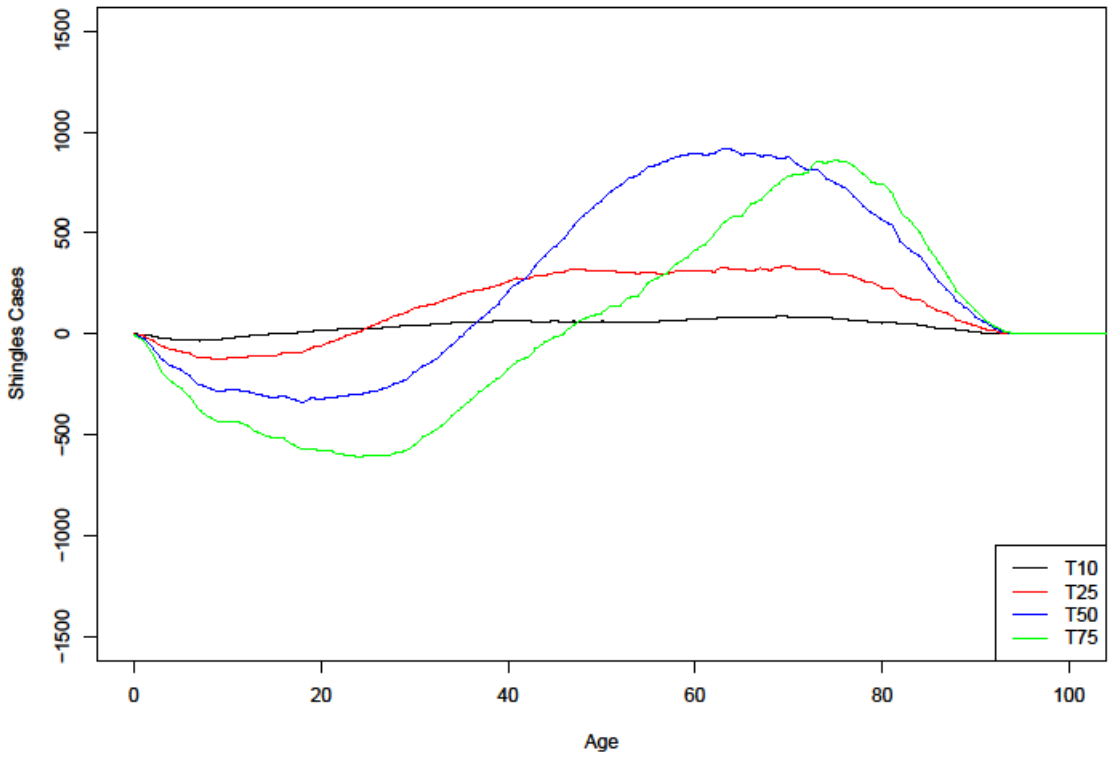

Figure 4.5. Mean cumulative count of shingles cases averted/added following vaccination by the age group and time point, baseline scenario (DoB= 5 year; WoI= 0.63) Positive number on the y-axis indicates the number of shingles cases added and negative number – the number of shingles cases averted.

4.4. Discussion

Our ABM successfully simulated chickenpox and shingles dynamics over time by creating a 500,000-person, distance based-contact network, with detailed representation of boosting and waning of immunity. We calibrated the model to six different scenarios for DoB and WoI for shingles, suggesting that many different quantitative values for these two unknown parameters are consistent with the empirical data. Based on this calibration, we determine that shingles incidence-post vaccination is highly sensitive to the values for both DoB and WoI, although all scenarios eventually led to a reduction in shingles incidence rates relative to baseline rates.

Infectious disease models can provide valuable insight into the complex relationship between chickenpox and shingles, allowing epidemiologists and biologists to test theories, study the impact of different parameters, and judge the outcomes of various interventions. To date the

majority of chickenpox and shingles models, including the only model representing a Canadian population [43] are aggregate compartmental models, which limit their flexibility and heterogeneity [20,44–48]. To our knowledge, one of the only individual-based model was created by Ogunjimi et al. [25] to combine within- and between host dynamics, and VZV immunological data to estimate boosting characteristics. Our model utilized their representation of the biological conditions for chickenpox and shingles infection and VZV-cell mediated immunity; however, it differs from the Ogunjimi model in several key ways [25]. Ogunjimi's model represented contacts using a probabilistic method whereas ours implemented a distance-based network and included an increased contact range for school-aged children [25,49]. The Ogunjimi model used a population that remained fixed in size and was based on Belgian demographics, while our model implemented an open and non-fixed population based on Alberta data, with realistic demographic changes over time. Furthermore, the Ogunjimi model assumed 100% vaccine effectiveness and incorporated only a one-dose chickenpox vaccination schedule, while ours included representations of vaccine attitudes as a dynamic predictor of vaccine coverage and probability of primary vaccine failure.

Our model concurs with previous models and biological studies that suggest exogenous boosting of VZV immunity is a likely factor in the limiting reactivation of VZV, as we were not able to recreate the empirical data observed in Alberta without incorporating some element of boosting [6]. Longitudinal immunological studies show individuals re-exposed to chickenpox, either on a one-time or continuous basis, have a corresponding increase in VZV-specific immunity [50–52]. However, these studies generally only look at the short-term immunological effects of boosting (up to one-year post-exposure) and not everyone is boosted following re-exposure, raising questions about the duration of immunity following boosting and the degree, number and quality of exposures needed to produce a boost of VZV-CMI [6]. A recent study showed that only 17-25% of grandparents who were exposed to chickenpox received a significant boost in VZV-specific immunity and that this boost typically lasted less than a year [53].

Using our agent-based model, we varied these unknown boosting parameters (e.g., DoB, WoI, degree and probability of boosting on contact) to see how those variations impacted the outcomes of chickenpox vaccination. By varying DoB and WoI simultaneously, we identified several boosting of immunity scenarios that could fit current Alberta data. In comparison, many

previous chickenpox and shingles models have made some strict assumptions about boosting of immunity, with the parameter values for the force or duration of immunity following boosting set high. For instance, Ouwens et al. [20] assumed that the force of boosting would be equal to the force of infection, while Brisson et al. [21] postulated each boost would result in 24 years of protection. It is perhaps not surprising that under these assumptions, many of the compartmental models predicted an increase in shingles following chickenpox vaccination.

Our results illustrated that the short-term increase in shingles cases following chickenpox vaccination is largely dependent on the DoB and WoI -- quantities whose values are still widely debated in the literature. Varying these values had a major impact on outcomes of chickenpox vaccination, with the percentage increase in incidence rate ranging between 4.8%-41.9% (25 years post-vaccination) between the most and least conservative DoB estimates. The only other study to vary the natural DoB, to our knowledge, was by Jan Van Hoek *et al.* [54], who found a short natural boosting and a longer shingles vaccine protection leading to variable increase in shingles following chickenpox vaccination. However, in this study, the DoB assumed one of only three values (7.5, 20, 42 years), only varied DoB in conjunction with shingle vaccine boosting, used a compartmental model and did not describe how they calibrated the model to empirical data [54]. Our experiments with lower durations of boosting predicted increases in shingles cases post-chickenpox vaccination smaller than previous models [21,46,55]. This is likely because, these DoB were significantly lower than previous models but are consistent with immunological assays used to measure the duration of immunity following boosting in grandparents as described in the study above [53]. Furthermore, the rate of boosting in our model was driven within an age- and distance- based transmission network rather than a random-mixing network, potentially limiting contacts that could produce a boost, which is supported by the fact that our average number of boosts per person was low at 1.83.

Our model results were congruent with other models that demonstrated, over a longer time horizon, shingles cases would decrease significantly following chickenpox vaccination. This decrease is because chickenpox vaccination decreases the burden of illness of chickenpox and the incidence of infection by VZV, thus reducing the population with dormant VZV, and producing a cohort effect as a greater and greater percentage of the population is vaccinated. Empiric studies post-chickenpox vaccination have started to show evidence of this cohort effect, with younger age groups who have received chickenpox vaccination having lower rates of

shingles than the corresponding age group prior to vaccination [56,57]. The ultimate drop in shingles cases will depend largely on what percentage of chickenpox vaccinated cohorts are susceptible to shingles, and therefore future studies should measure the likelihood of the vaccine strain of VZV remaining latent in the body, as well as its ability to reactivate.

To date, empirical findings drawn from the era following introduction of chickenpox vaccination are largely inconsistent, making it difficult for policy-makers to know the continued impact of the chickenpox vaccine. While some studies show an increase in rates of shingles following the implementation of chickenpox vaccination, similar studies have shown that this increase started prior to vaccination, and other studies have found rates have stayed the same following vaccination [4,56]. Different contact and boosting patterns (e.g. number of boosting events, age at which boosts occur, age of chickenpox infection) in different countries may also shape some of the observed differences in the age-specific incidence rates of shingles by country and potentially the impact of chickenpox vaccination by country [47]. Two Canadian studies argued that the incidence rate of shingles was increasing prior to chickenpox vaccination implementation and has stayed consistent following the implementation; however, such studies took place only seven and eight years following vaccination, and one study did not adjust for age [4,56]. Our model demonstrated that at a lower DoB and higher WoI, the perceivable impact on shingles rates would be quite small, increasing from 383 cases per 100,000 person-years to 406 per 100,000 person-years 10 years after chickenpox vaccination. This small increase may be difficult to measure or observe in empirical data where other factors influence the shingles rates (e.g., shingles vaccination, co-morbid infections, ageing of the population). We did not include some of the key determinants of shingles epidemiology in our model, including shingles vaccination and the impact of co-morbidities, making the comparison of empirical data and our model findings difficult.

Our model produced some interesting secondary findings and observations. First, as with previous models, we found it challenging to account for the rate of shingles infection seen in the youngest age group [25]. Russell et al. [4] shows a small but sudden increase in the rate of shingles infection in one- to four-year-olds. We theorized that a substantial proportion of these cases could be due to immunocompromising conditions in young children that may place them at a greater risk of developing shingles. However, it would be interesting to further explore if these individuals alone could account for this increase and if this is a trend that is found across

countries. Furthermore, we found that varying chickenpox vaccine coverage (by changing vaccine attitudes within 10%) had only a minor impact on shingles incidence. However, greater changes to vaccine coverage levels would eventually realize larger impacts on shingles incidence. One next step may be to test the impact of changing coverage rates over time, as experience illustrates that coverage rates may decrease as individuals become increasingly accustomed to the vaccine.

Although our model is one of the most detailed extant representations of the interaction between chickenpox and shingles, it is subject to limitations. First, we ran our model on a population of 500,000, raising the question of applicability to larger populations. However, we observed very little deviation in our findings when we ran the model on 50,000 vs. 500,000, suggesting a robustness of results to broad ranges in population size. Second, following a review of the literature, we decided not to include endogenous boosting (i.e. self-boosting of VZV when the virus attempts to reactivate within an individual), as the relevance of endogenous boosting is debated in the literature and Ogunjimi et al. [25] found it insignificant. Third, we had difficulty accounting for shingles in younger age groups, and therefore had to adapt our model to fit Canadian data. Fourth, we were only able to vary a couple of the parameters relevant to the boosting of immunity; future research should further explore the impact of changing multiple boosting parameters (e.g., probability of boosting on contact by age). Fifth, we did not include the shingles vaccine in the analysis because we wanted to focus on the effect of chickenpox vaccine on natural shingles infection. However, in future analysis, the ability of the shingles vaccine to mitigate any increases in shingles cases following chickenpox vaccination will be important to explore. It is for this reason our model includes the shingles vaccine functionality. Finally, we used a stylised distance-based network to represent transmission of infection and did not implement a truly age-dependant contact matrix.

Future research and agent-based modelling should focus on studying some of the remaining unknowns surrounding the mechanisms of VZV reactivation, waning and boosting of immunity. ABMs could explore how changing the contact patterns alters the number and type of boosting events, and how this variation may explain the differences in shingles incidence both before and after chickenpox vaccination in different countries. Moreover, there should be ongoing comparison of model results and empirical findings post-chickenpox vaccination, so we can update model parameters to fit with changing data. Our findings highlight the importance of

not only studying when and if boosting occurs, but also the level of protection it confers on the individuals. While Ogunjimi et al. [53] provides a good start to measuring the quantifiable impacts of boosting, studies should measure the longer-term immunological impacts of re-exposure and how those measurements translate to risk of reactivation. Furthermore, future research and models may want to look at the impact of other disease and population factors on the changing epidemiology of shingles, including immunocompromising conditions, immunocompromising drug therapies, co-morbid infections (e.g., CMV), and stress.

4.5. Conclusion

Our model highlights the importance of not simply knowing when and if the VZV boosting events occur but the specific duration of immunity following boosting, as these values can impact the effect of chickenpox vaccination on shingles incidence over time. Our study suggests that over the longer time period, there will be a reduction in shingles incidence driven mostly by the depletion of the source of shingles reactivation, assuming only a low percentage of chickenpox vaccinated individuals are at risk of VZV reactivation. These findings suggest that in the long-term a universal chickenpox vaccine would be a good policy to reduce both chickenpox and shingles cases. However, in the short to medium term some age cohorts may experience an increase in shingles incidence. Studies exploring Canadian's willingness to pay to avoid chickenpox and shingles may provide insight into which trade-offs are worthwhile. Our model offers a platform to further explore the relationship between chickenpox and shingles, including analyzing the impact of different chickenpox vaccination schedules and cost-effectiveness studies.

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CHAPTER 5- THE OPTIMAL SCHEDULE FOR CHICKENPOX VACCINATION IN CANADA: EXPLORING THE IMPACT OF TIMING, COVERAGE AND WANING OF VACCINE IMMUNITY ON DISEASES OUTCOMES USING AN AGENT-BASED MODEL

My contributions to this manuscript included conceptualizing the model updates, conceiving and designing the study, running the experiments, analysing and interpreting the findings and manuscript preparation. Wade McDonald, updated the previous model to test two different vaccination schedules, added results outputted from the model, and oversaw the running of the model experiments. Dr. Nathaniel Osgood, aided in the conception and the design of the study, and oversaw all model adaptations and model runs. Dr. Alexander Doroshenko aided in the conception and design of the study.

This chapter builds on the previous chapter by shifting the focus from the impact of chickenpox vaccine on shingles to its effect on chickenpox. We used the agent-based model described and calibrated in **Chapter 4** to test the effectiveness of the chickenpox vaccine in preventing chickenpox disease, as well as its impact on breakthrough rates, physician visits and age of infection. Furthermore, policy-makers both in Canada and worldwide are interested not only in the effects of implementing the vaccine but also in understanding whether there is optimal timing for delivery of the chickenpox vaccine. The question of the most appropriate chickenpox vaccine schedule is especially relevant in Canada where the vaccine has been implemented for many years, with many provinces having different eligibility ages for first and second dose chickenpox vaccination. Therefore, in this chapter we compare the effectiveness of two chickenpox vaccine schedules common in Canada, Schedule long dosing interval at 12 months and 4-6 years, and Schedule short dosing interval at 12 months and 18 months.

5.1. Introduction

The scheduling of a vaccine is often a complex choice for health program administrators. Many factors should be taken into consideration when determining the most appropriate approach to implementing a vaccine in a population, including (1) the simplicity of implementation (e.g. are there other vaccines already provided at that age?; when will parents already be going to see a health care professional?); (2) the types of vaccines licensed (e.g. do program administrators need to consider the timing of other antigens included in a combination vaccine); (3) the effectiveness of various schedules (e.g. whether one schedule prevents more disease and hospitalizations overall, or prevents disease in a high risk group?); (4) the costs associated with different schedules; (5) public opinion and preference; (6) adverse events associated with the type of vaccine and the age it is administered (e.g. febrile seizure) [1].

Chickenpox is a childhood disease caused by the varicella zoster virus (VZV). Prior to vaccination chickenpox caused an estimated 350,000 cases per year in Canada, a rate of 11.9 cases per 1,000 persons per year [2]. While some countries, including the US and Canada, have implemented universal varicella vaccination programs, many countries are still debating the utility of including chickenpox in their routine immunizations [3]. Even in countries where the chickenpox vaccine is part of the universal vaccine schedule, questions remain about the most efficient and effective way to deliver the vaccine.

The debate over chickenpox vaccine schedules is evident in Canada, where all provinces and territories have some form of universal chickenpox vaccine, but there were eight different schedules across the country in 2017 [4]. Provinces and territories recognize that variations in how chickenpox vaccine is administered in the population can impact a range of disease and vaccination outcomes, such as the risk of febrile seizures [5], the number of outbreaks of chickenpox and the number and severity of breakthrough cases [6]. In Alberta, along with Manitoba, there is a combined MMRV (measles, mumps, rubella, varicella) two-dose schedule, with the first dose offered at 12 months and the second dose at 4-6 years. In comparison, Saskatchewan, Prince Edward Island, Newfoundland and New Brunswick, offer MMRV at 12 months and 18 months. Ontario (V- 15 months, MMRV- 4-6 years), British Columbia (V-12 months; MMRV- 4-6 years) and Quebec (MMRV-18 months; V- 4-6 years) each have their own individual schedules. As is evident in the above examples, each of these schedules implement a different number of doses, various types of vaccines (i.e. combination vaccine MMRV or single

antigen vaccine varicella), and can alter the timing for both the first dose (12 months or 15 months) and second dose (18 months or 4-6 years) [4]. However, very little is known about which schedule is the most effective at preventing chickenpox disease now and into the future [7].

Appropriate vaccine scheduling is only one of a variety of other unknowns surrounding the chickenpox vaccine. For instance, the coverage varies by region and therefore it would be valuable to understand how different coverage rates may impact herd immunity and population-level disease outcomes [8]. Moreover, there is a wide range of plausible estimates for primary chickenpox vaccine failure, and the rate at which vaccine immunity wanes remains largely unknown. Currently, researchers are unsure of the relative impact of these two variables on chickenpox disease outcomes in the long term [9–12]. Therefore, it is important researchers explore how these variables and other unknown factors may impact the effectiveness of the chickenpox vaccine overall and the effectiveness of various vaccine schedules

Infectious disease models are one of the best methods to test the effectiveness of different interventions over a long time-frame. These models also allow researchers to ask 'what-if' questions about the disease and the interventions. Using infectious disease models, researchers can explore the sensitivity of model results to changes in certain parameters (e.g. how varying waning of chickenpox vaccine immunity rates may impact the vaccine's ability to prevent disease over time). Agent-based models (ABMs) are particularly useful as they characterise each individual in the population (agent), and therefore present the individual-level factors that change an individual's risk of infection and vaccination over time, such as their vaccine attitudes, their history of disease and their age.

The primary objective of this study was to determine the impact of two different chickenpox vaccine schedules on chickenpox disease outcomes and epidemiology in Alberta. Using an ABM of chickenpox disease and vaccination calibrated to Alberta demographics, vaccination coverage and disease incidence rates prior to vaccination (chickenpox and shingles), we tested the impact of these two schedules across four different time periods (10, 25, 50 and 75 years). Furthermore, we measured how different assumptions for primary and secondary vaccine failure, as well as vaccination attitudes and coverage rates, may alter the effectiveness of chickenpox vaccination overall and the effectiveness of two vaccine schedules.

5.2. Methods

We developed an ABM of chickenpox and shingles infection and transmission, along with chickenpox vaccination, using AnyLogic® Professional software (version 8.1) (**Data reference 1).** In-depth descriptions of the model structure, agent characteristics, distance-based contact network, and initial parametrization and calibration are available in **Chapter 4**. We implemented a 75-year burn-in period, to allow the chickenpox and shingles infection rates to reach equilibrium and to ensure we had a distribution of individuals at risk of shingles. At 100 years we initiated chickenpox vaccination and gathered data for 75 years post-vaccination.

5.2.1. Model structure and agent characteristics

We used the chickenpox and shingles ABM developed in **Chapter 4** to represent the spread of chickenpox through a population over time. Agents were placed within a stylised environment of 500,000 persons. We used a distance-based contact network to create connections (i.e. number of other agents one agent is connected to; *connectionRange_Norm*) and contacts (number of times connected agent contact each other; *baseContactRate_Norm*) among agents. Younger persons, aged one to nine, were considered our preferential age group, and therefore connected with agents of the same age farther away (*connectionRange_Pref*) and a higher number of contacts (*baseContactRate_Pref*). Finally, we included an element of exogenous infection where an individual could be infected with chickenpox from outside our modelled population (*ExogenousInfectionRate*); this model element allowed for the representation of disease importation into the population. It was through these connections and assumptions that chickenpox disease spread.

We chose to use an ABM because it can account for, and represent in detail, a variety of disease dynamics prominent in chickenpox and shingles, including herd immunity, waning of VZV immunity, shifting of age of infection, breakthrough illness and varying transmissibility depending on type of infection (e.g. breakthrough, shingles), among others. ABMs are stochastic and account for randomness in disease infection; therefore, they can accurately replicate the patterns of outbreaks and recovery associated with infectious diseases. ABMs can capture non-random interactions within a network (e.g. interaction based on distance), where contacts may be recurrent and sustained over extended periods of time, much like real-life. ABM allow researchers to capture the vaccine, disease and health service histories of agents in detail, which can significantly alter their risk of infection and can help us capture a variety of disease and

vaccination outcomes. For instance, in our ABM it is possible to calculate the number of breakthrough cases of chickenpox, determine if they are due to primary or secondary vaccine failure, and select a certain percentage of the breakthrough cases to get a weaker form of chickenpox, with a shorter duration of infection and transmission, and lower risk of hospitalization and death.

Our ABM includes four different statecharts, which determines an agent's current disease (Disease statechart) and vaccination state (Vaccination statechart), their age and risk of mortality (Demographic statechart), as well as their health service utilization (Hospitalization statechart). (**See Figure 4.2, Chapter 4**)

5.2.2. Model parameterization

We parameterized the model through a review of the literature, including peer-reviewed articles on modelling, epidemiology, effectiveness and immunology, population-level health administration data (e.g. vaccine coverage) and demographic data. (e.g. mortality and fertility rates). See **Table 4.1 in Chapter 4** for a list of the parameters included in the construction of the chickenpox model. A full list of the parameters' values used in this analysis is available in **Appendix F**.

5.2.3. Chickenpox and shingles disease and transmission

The disease statechart determines an agent's disease-state and therefore risk of infection from either chickenpox or shingles, states include 'maternalAntibody', 'susceptible', vaccine protected 1 ('Protected1') and 2 ('Protected2'), susceptible to breakthrough ('susceptibleBreakthrough'), infected chickenpox ('infectedCP'; 'infectedWeaklyCP'), recovered chickenpox ('recoveredCP'), 'infectedShingle', post-herpatic neuralgia ('PHN'), and 'recoveredFromShingle', amongst others (**See Figure 4.2, Chapter 4**). A more detailed description of how chickenpox and shingles disease are acquired and transmitted in our model, and the model representation of boosting and waning of VZV immunity and their impact on chickenpox and shingles incidence, both before and after chickenpox vaccination, is presented in **Chapter 4**.

5.2.4. Chickenpox vaccination

The chickenpox vaccination statechart determines when an agent is due for their first and second doses of the chickenpox vaccine, and whether the agent ends up receiving each dose of

the vaccine. The ABM can model the two main vaccination schedules used in our analysis (i.e. a schedule with a long dosing interval [schedule LDI]- 12 months/4-6 years and a schedule with a short dosing interval [schedule SDI]- 12 months/18 months) by setting the *CPVaccStrategy* variable, although many other vaccine schedules could be tested by changing the *dueFor1stDose* and *dueFor2ndDose* parameters. Based on the pre-set vaccination schedule, agents receive a message to get vaccinated when they reach a certain age. The agents' probability of getting vaccinated (e.g. transitioning into *received1stDose* instead of *no1stDose*), is then determined by their vaccine attitude (i.e. *vacc_rejector*, *vacc_hesistant* and *vacc_acceptor*). All these factors ultimately govern the coverage rate of chickenpox vaccine at first and second dose, which is an output of the model.

Whether an individual is effectively protected against chickenpox following vaccination is determined in the disease statechart, where agents have a certain risk of primary vaccine failure upon receipt of the first and second dose vaccine (*probabilityOf1stDoseEffective; probabilityOf2ndDoseEffective*). If the first dose is effective the agent transitions to 'Protected1', and if it is not effective they transition to 'susceptibleBreakthrough'; if the second dose is effective they can transition from Protected1' state to 'Protected2', or from 'susceptibleBreakthrough' to 'Protected1'. We also included the possibility for secondary vaccine failure, and therefore agents in 'Protected1' had a certain probability per year (*waningOfImmunityRateCPvacc*) of transitioning to 'susceptibleBreakthrough', and agents in 'Protected2' had a certain risk per year (*waningOfImunityRateCPVacc2*) of transition into the 'Protected1' state.

Thus, agents who are vaccinated but not protected from chickenpox, either due to primary or secondary vaccine failure gather in the 'susceptibleBreakthrough', state where they have the same risk of being infected on contact as those in the 'susceptible' state. However, if they are infected they have a certain probability of being 'infectedWeaklyCP' instead of acquiring the full infection ('infectedCP'). Adding an 'infectedWeaklyCP' state allowed us to capture the lower risk of serious infection in breakthrough cases; therefore, in this state there was no risk of dying or being hospitalized with chickenpox [9].

By using the disease and vaccination elements described above our ABM could capture a wide range of outcomes, including the rate and percent of breakthrough illness in the population, the effectiveness of the vaccine in preventing disease and the number of agents in the population

that have full chickenpox infection versus an attenuated infection. Representing both primary and secondary vaccine failure independently also gave our model the flexibility to separately test the effect of each of these variables on chickenpox disease outcomes.

5.2.5. Healthcare utilization

The disease and hospitalization statecharts in our ABM capture a variety of disease outcomes, including chickenpox and shingles incidence and age of infection, as well as deaths (*probabilityOfComplicationDeathCP*). Furthermore, we can evaluate various health care utilization outcomes; for instance, when an agent is infected with chickenpox, they have a certain probability of visiting a physician (*probGPVisitCP*), going to the emergency room (*probEDVisitCP*) or being hospitalized (*tfFracHospitalizedCPbyAge*). An agent's probability of being hospitalized for chickenpox is based on their age, with a higher risk of hospitalization in older age groups. Each agent who received an effective first dose of chickenpox vaccination also had a certain risk of having an adverse event, specifically a febrile seizure (*probFebrileSeizure*).

5.2.6. Shingles disease

Based on our findings in **Chapter 4,** we decided to make the following assumptions about shingles: a duration of immunity following boosting of five years and a waning of VZV immunity coefficient of 0.63. The waning of immunity coefficient, in combination with the waning of immunity rate, determine how quickly an agent's immunity to VZV wanes immediately following chickenpox infection. The duration of immunity following boosting values represents the number of years (5 years) an agent's VZV immunity would be boosted if they came into effective contact with VZV (i.e. a chickenpox or shingles case) and if they are recovered from chickenpox. In combination these values determined the likelihood of an agent getting shingles following chickenpox infection, as well as the timing of the infection. We selected these values for duration of immunity following boosting and waning of immunity because they produced the best model to empirical data fit in the pre-vaccine model calibration completed in **Chapter 4.**

5.2.7. Model validation

Our model calibration prior to vaccination was completed in **Chapter 4**. In that chapter we confirmed that the overall age-specific incidence for chickenpox and shingles in our model was consistent with what was observed in Canada (Alberta and Ontario) prior to vaccination

[13,14]. To check the consistency of our model outcomes to post-vaccination outcomes in this chapter, we compared the model results to what was observed in the Canadian literature following chickenpox vaccination.

We compared the model data (for both schedule LDI and schedule SDI chickenpox vaccination) to empirical data for five different outcome variables: percent decrease in chickenpox hospitalization, percent decrease per year in physician visits, first and second dose chickenpox vaccine effectiveness (i.e. percentage reduction in risk of disease among vaccinated persons relative to unvaccinated persons) and vaccine coverage, and finally the percent of total cases that are breakthrough cases. The aim of these tests was not to precisely reproduce the empirical data following chickenpox vaccine but to show our results were consistent with the Canadian literature.

5.2.8. Main experiment

The main objective of this study was to test the impact of two different chickenpox vaccine schedules on chickenpox disease outcomes and therefore to determine whether vaccination timing significantly influenced disease outcomes. A secondary objective of the analysis was to test the impact of chickenpox vaccine into the future, to measure how current assumptions about vaccine effectiveness and coverage would influence disease outcomes 75 years following the implementation of the chickenpox vaccine. Therefore, for the main experiment we tested three different scenarios, (1) no vaccination- we ran the model for 75 years (100 year to 175 year) following the 75 year burn in period without introducing vaccination; (2) schedule LDI- we introduced vaccination at year 100 and ran the model for 75 years, with children receiving first dose chickenpox vaccination at 12 months and second dose vaccination between 4-6 years; (3) schedule SDI- we introduced vaccination at year 100 and ran the model for 75 years, with children receiving first dose chickenpox vaccination at 12 months and second dose vaccination at 18 months. All other variables remained constant across all three scenarios.

We tested the impact of these three different scenarios on four disease outcomes, chickenpox incidence, breakthrough rate, shingles incidence and age of chickenpox infection. For each scenario in the main experiment we conducted a minimum 30 runs. Based on the previous sample calculation describe in Chapter 4, and practical considerations (i.e. model run time) we decided to maintain our sample size at 30 paired runs minimum. By pairing runs across the three scenarios we could ensure consistency in the random seeds used to populate the model

(i.e. all models started with the same values for the parameters and variables). We calculated a 95% predictive interval (2.5^{th} and 97.5^{th} percentile) across all model runs, for each disease outcome of interest. Furthermore, we tested for statistically significant difference between schedule LDI and schedule SDI for all model outcomes using the non-parametric Kolmogorov-Smirnov test.

5.2.9. Sensitivity analysis

Sensitivity analyses allowed us to test our model assumptions and study their impact on overall disease outcomes 75 years post-vaccination. For the first sensitivity analysis we moved 15% of vaccine hesitant individuals to vaccine acceptors which resulted in higher vaccination coverage (vaccine attitude high), and subsequently moved 15% of hesitant individuals to vaccine rejectors, resulting in lower vaccination coverage (vaccine attitude low). Second, we varied primary vaccine failure from 9% to 24% for first dose vaccination and 5% to 16% for second dose vaccine, the lowest and highest values for vaccine failure reported in reviews of the literature. [11,12,15–17] Third, we compared disease outcomes between schedules when we lowered the waning of chickenpox vaccine immunity for both first and second dose to zero and subsequently raised it to 5% per year. We ran a minimum of 30 paired model runs of schedule LDI and schedule SDI for each sensitivity analysis and measured the 95% predictive interval to see if changing these parameters had an impact on the model outcomes for each schedule.

5.3. Results

5.3.1. Model validation

Our model findings at 10 years post-vaccination were consistent with empirical data. All model results for the five different outcome variables for schedule LDI and schedule SDI as compared to empirical data are presented in **Table 5.1**. The 95% predictive interval (2.5 and 97.5 percentile) for schedule LDI/schedule SDI and the confidence intervals for empirical data overlapped for percent decrease in chickenpox hospitalization, physician visits per year and coverage rates. Coverage rates ranged from 85.2% to 85.3% for the first dose, and 73.8% to 74.4% for the second dose. The predictive intervals and confidence intervals for vaccine effectiveness for model data and empirical data largely overlapped; however, we observed a slightly lower effectiveness in our first dose vaccination and a slightly higher effectiveness in our

second dose vaccination. Our breakthrough cases for schedule SDI were slightly lower than those reported in the literature.

Table 5.1. Vaccine and disease outcome variables 10 years post-chickenpox vaccination in comparison to empirical data from the literature

Parameter	**Model Data-Schedule LDI[1,2] (95% predictive interval)**	**Model Data-Schedule SDI[1,2] (95% predictive interval)**	**Empirical data (95% CI)[3]**	**Ref**
Chickenpox hospitalization (% decrease)	80% (77%, 86%)	81% (79%, 84%)	79% (74%, 82%)	[18]
Chickenpox physician visits (% decrease per year)	8.0% per year (7.7%, 8.6%)	8.2% per year (8.0%, 8.4%)	<1 year: 7.7% 1-4 years: 9.1% 5-11 years: 8.4% >12 years: 8.4%	[19]
Vaccine effectiveness - 1st dose - 2nd dose	 76% (72%,80%) 94% (92%, 97%)	 79% (74%, 84%) 96% (95%, 98%)	 81% (78%, 84%) 92% (88%, 95%)	[9]
Breakthrough (% of total cases)	2.0% (1.1%, 3.2%)	0.7% (0.5%-1.5%)	2%-3.1%	[18,20]
Vaccine Coverage	1st dose: 85.1% (84.7%, 85.6%) 2nd dose: 73.9% (73.0%, 74.7%)	1st dose: 85.4% (84.8%, 85.9%) 2nd dose: 74.6% (73.8%, 75.6%)	1 dose: 86.7% 2nd dose: 75.3%	[21]

[1]Model data is presented as medians 10 years post-vaccination to compare to a time-period similar to that reported in the empirical data.
[2]Schedule LDI is 1st dose MMRV at 12 months and 2nd dose at 4-6 years, and Schedule SDI is first dose of MMRV at 12 months and second dose at 18 months.
[3]If available the 95% CI from the empirical study is reported

5.3.2. Main experiment

Generally, we found that chickenpox vaccination led to a significant decrease in chickenpox incidence at 10, 25, 50 and 75 years post-vaccination implementation (**See Table 5.2, Figure 5.1**). While the lowest chickenpox incidence occurred at 75 years post-vaccination, the first 10 years had the most dramatic decrease. Following the initial dramatic decrease in chickenpox cases our model predicted the average chickenpox incidence rate staying in relative equilibrium, with period but small outbreaks of the disease (**See Figure 5.1**). Moreover, we saw a dramatic increase in the average age of chickenpox infection following vaccination. In this case the average age continued to increase consistently over time, with the oldest age of infection being 75 years post-vaccination.

We observed relatively minor differences when we compared chickenpox and shingles disease outcomes between the two vaccination schedules (**See Table 5.2, Figure 5.1**). Schedule SDI led to a slightly larger decrease in chickenpox cases in comparison to schedule SDI; however, the 95% predictive intervals overlapped. When comparing the paired sets directly, 100% of paired runs found that schedule LDI resulted in a higher chickenpox incidence rate than schedule SDI. The absolute difference in incidence rate was 0.1 cases per 1,000 person-years (after 75 years). Therefore, in the Alberta based on these numbers schedule LDI would prevent approximately four hundred more chickenpox cases per year than schedule SDI. At the same time, we observed overlapping 95% predictive intervals for the shingles incidence between the two schedules, suggesting no significant difference. However, 75% of paired model runs found schedule SDI had a slightly higher shingles incidence than schedule LDI. Both the number of breakthrough cases and the age of chickenpox infection were strikingly different when examining the two vaccine schedules (**Table 5.2**). For instance, at each time point post-vaccination, age of chickenpox infection was consistently and significantly higher in schedule SDI (100% of paired model runs), while there were significantly more breakthrough cases with schedule LDI (100% of paired model runs). In fact, over the 75 years post-vaccination schedule LDI had a breakthrough rate 62% higher than schedule SDI.

Table 5.2. Health outcomes by time since vaccination and scenario over 37 paired model runs, median (95% predictive interval)

	Time since vaccination				
	10 years[1]	**25 years**	**50 years**	**75 years**	**P-value**[2]
Chickenpox incidence per 1,000 person-years					
- No vaccine	12.6 (11.5, 13.8)[4]	12.2 (11.6, 12.8)	12.2 (12.0, 12.5)	12.1 (12.0, 12.3)	-
- Schedule LDI[3]	2.5 (1.6, 3.2)	1.2 (0.8, 1.5)	0.79 (0.58, 0.93)	0.60 (0.46, 0.70)	Ref
- Schedule SDI[3]	2.3 (1.3, 2.8)	1.1 (0.7, 1.3)	0.66 (0.45, 0.79)	0.50 (0.36, 0.59)	<0.001
Breakthrough rate per 100,000 person-years					
- Schedule LDI	5.3 (3.2, 6.9)	4.8 (4.1, 5.2)	6.7 (6.2, 7.3)	7.8 (7.0, 8.6)	Ref
- Schedule SDI	1.6 (1.3, 2.1)	2.0 (1.8, 2.2)	3.7 (3.5, 4.0)	4.8 (4.6, 5.1)	<0.001
Shingles incidence per 1,000 person-years					
- No vaccine	4.0 (3.9, 4.0)	4.0 (4.0, 4.0)	4.0 (4.0,4.1)	4.0 (4.0, 4.1)	-
- Schedule LDI	4.4 (4.3, 4.5)	4.9 (4.9, 5.0)	4.9 (4.9, 5.0)	4.2 (4.2, 4.2)	Ref
- Schedule SDI	4.4 (4.4, 4.5)	4.9 (4.9, 5.0)	4.9 (4.9, 5.0)	4.2 (4.1, 4.2)	0.018
Median Age of chickenpox infection					
- No vaccine	9.7 (9.5, 9.9)	9.8 (9.7 9.9)	10.0 (9.8, 10.1)	10.1 (10.0, 10.2)	-
- Schedule LDI	12.5 (12.0,13.3)	17.4 (16.9, 18.1)	23.6 (23.0, 24.2)	28.4 (27.9, 29.0)	Ref
- Schedule SDI	13.6 (13.0, 14.1)	18.9 (18.5, 19.6)	26.0 (25.2, 26.5)	31.2 (30.4, 32.0)	<0.001

[1]All time-periods represented the cumulative number started at year 0 (first year of vaccination).

[2]P-values compare schedule LDI and schedule SDI for statistical significance using Kolmogorov-Smirnov test at time 75 years.

[3]Schedule LDI is 1st dose MMRV at 12 months and 2nd dose at 4-6 years, and Schedule SDI is first dose of MMRV at 12 months and second dose at 18 months.

[4]All point estimates are medians and ranges are presented as 95% predictive intervals (2.5th percentile and 97.5th percentile)

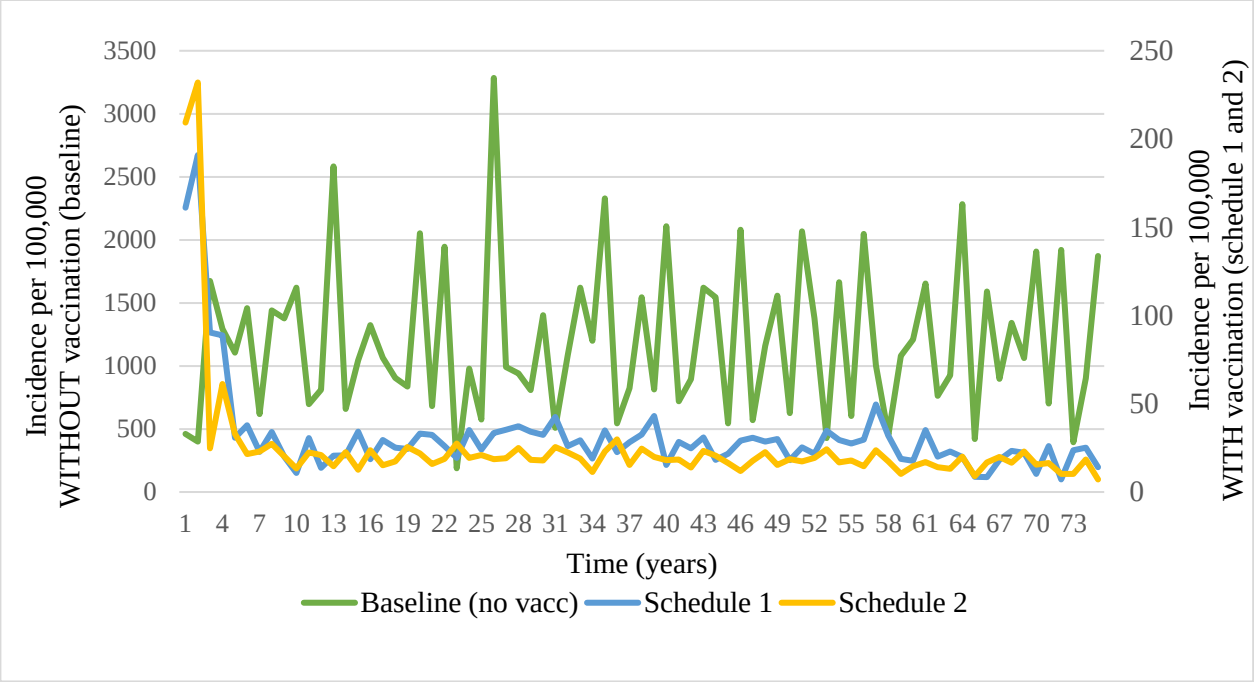

Figure 5.1. Chickenpox incidence (per 100,000 person-years) over time by scenario

5.3.3. Sensitivity analysis

Generally, we found that changing the primary vaccine failure rate or altering the vaccine attitudes (i.e. changing vaccine coverage) in our population did not impact our overall findings. While decreasing and increasing primary vaccine failure lead, respectively, to a significant jump and reduction in breakthrough cases, the overall incidence of chickenpox stayed relatively consistent. Increasing the percentage of 'rejectors' in our population did decrease the coverage rates for first (75% for both schedules) and second dose (66% for both schedules) chickenpox vaccine substantially (approximately 10% reduction in coverage) and increased the incidence of chickenpox by 30-40% relative to baseline. However, this only translates to an increase of 0.3-0.4 cases per person-year. Increasing the percentage of 'acceptors' in our population had a smaller, non-significant effect, with coverage for both schedules increasing to 89% and 80% for first and second dose, respectively. Chickenpox incidence rates for this scenario stayed very similar to baseline values. Increasing the waning of immunity rate to 5% per year had the biggest impact on chickenpox incidence, with over two times as many cases with the higher waning immunity rate in comparison to baseline. Furthermore, the number of breakthrough cases increased to a very high rate, with 47-81 breakthrough cases per 100,000 person-years.

Table 5.3. Health outcomes for different sensitivity analyses over 30 model runs, median (95% predictive interval)

	Waning rate low[1]	Waning rate high	Primary vaccine failure low[2]	Primary vaccine failure high[2]	Vaccine attitude low[3]	Vaccine attitude high	Baseline
Chickenpox incidence per 1,000 person-years							
- Schedule LDI[4]	0.5 (0.4, 0.7)	1.6 (1.5, 1.8)	0.5 (0.4, 0.6)	0.7 (0.5 0.8)	1.1 (1.0, 1.2)	0.6 (0.4, 0.7)	0.6 (0.5, 0.7)
- Schedule SDI[4]	0.4 (0.3, 0.6)	1.0 (0.9,1.2)	0.4 (0.3, 0.6)	0.5 (0.4, 0.7)	0.8 (0.6, 0.9)	0.5 (0.3, 0.6)	0.5 (0.4, 0.6)
Chickenpox breakthrough rate per 100,000 person-years							
- Schedule LDI	5.2 (4.9, 5.6)	82 (76, 88)	3.4 (3.2, 3.6)	11 (11, 12)	20 (19, 22)	9.0 (8.6, 9.7)	7.8 (7.3, 8.3)
- Schedule SDI	3.1 (2.8, 3.3)	47 (44, 50)	2.3 (2.2, 2.5)	6.9 (6.7, 7.2)	12 (11, 13)	6.2 (5.7, 6.4)	4.8 (4.6, 5.1)
Age of chickenpox infection (years)							
- Schedule LDI	28 (27, 28)	27 (27, 28)	30 (30, 31)	28 (27, 28)	26 (25, 26)	29 (28, 29)	28 (28, 29)
- Schedule SDI	31 (30,31)	29 (29, 29)	33 (32, 33)	30 (30, 31)	28 (27, 28)	31 (31, 32)	31 (31, 32)

[1]For 'Waning rate low' the first and second dose vaccine waning of immunity rate was set to zero; for 'Waning rate high' the first and second dose waning of immunity rate was set to 5%.

[2]'Primary vaccine failure low' was set to 9% for first dose and 5 % for second dose; 'Primary vaccine failure high' was set to 24% for first dose and 16% for second dose.

[3]For 'Vaccine attitude high' we changed the vaccine attitude weights to acceptor= 80%, hesitator= 15%, rejector= 5%; For 'Vaccine attitude low' we changed the vaccine attitude weights to acceptor= 65%, hesitator= 15%, rejector= 20%.

[4]Schedule LDI is 1st dose MMRV at 12 months and 2nd dose at 4-6 years, and Schedule SDI is first dose of MMRV at 12 months and second dose at 18 months.

5.4. Discussion

Using our ABM we were able to replicate the epidemiology of chickenpox and shingles both prior to vaccination and following its implementation. Our model results were validated by findings in the literature, including chickenpox vaccine effectiveness in preventing infection, as well as the percent decrease in chickenpox hospitalizations and physician visits following vaccination implementation [9,13,18–20]. While our model results found a slightly lower effectiveness in first dose vaccination and a slightly higher effectiveness in second dose vaccination in comparison to the literature, we postulate this finding may be explained by the fact that there is a large amount of variability in vaccine effectiveness estimates in real-world studies [9]. Furthermore, we observed a low breakthrough rate for schedule SDI; however, as most jurisdictions, including the United States, offer the second dose of chickenpox at 4-6 years of age, it is perhaps not surprising that the rates are more consistent with schedule LDI. Furthermore, the number and rate of breakthrough cases can change dramatically as a result of time since vaccination, as well as the case definition used to identify breakthrough cases, and the surveillance and case-identification process utilized to monitor cases (e.g. active surveillance during an outbreak or passive surveillance through physician visits). Our model produced coverage rates similar to what is observed in Alberta for chickenpox vaccination using a distribution of vaccine acceptors, hesitants and rejectors in our population [21]. Using the ABM we tested the effectiveness of chickenpox 75 years into the future, along with the effectiveness of two diverse vaccine schedules.

Previous models have explored the effectiveness of the chickenpox vaccination in preventing disease [22–25], with two providing a Canadian-focus [26,27]. In the most recent Canadian chickenpox modelling study, Brisson et al. [27] used an age-structured transmission model to predict the impact of both a one-dose and two-dose chickenpox vaccination schedule. His model predicted an initial rapid decrease in chickenpox cases following implementation of a two-dose vaccination, reducing cases of chickenpox by 72-97% over 80 years [27]. These findings are similar to our model predictions, which also had a substantial fall in chickenpox incidence, specifically a reduction of approximately 95% of chickenpox cases, 75 years following vaccination introduction.

However, we noted some difference between our model findings and the Brisson model [27]. For instance, the Brisson model predicted a slow rise in chickenpox cases 40 years into the

vaccine program, whereas our model at around the same time point showed a steady number of chickenpox cases, with the incidence staying in equilibrium [27]. Furthermore, the Brisson model consistently predicted a substantial outbreak of chickenpox 10 years after vaccine introduction [27]. Our model also predicted outbreaks of chickenpox; however, we did not observe one large chickenpox outbreak but small and periodic outbreaks of cases, demonstrating low but sustained transmission of chickenpox in the ABM population. We postulate the perpetuation of chickenpox in our model is likely due to three factors; (1) the ability of shingles and breakthrough infection to transmit chickenpox, although at a lower rate, (2) the inclusion of exogenous infection in our model and (3) the fact that vaccine immunity may wane over time.

Pivotal differences in modelling techniques and assumptions between this study and Brisson et al. [27] may further explain some of the conflicting findings. First, we fit our ABM to real-world data from Canada 10 years following the implementation of the chickenpox vaccination, including decrease in hospitalizations and physician visits, along with number of breakthrough cases and coverage rates. In comparison, Brisson et al. [27] generally used data from clinical trials to calibrate his model. We built on the Brisson model by updating parameters estimates based on current literature, including primary and secondary vaccine failure, coverage rates, as well as boosting and waning of VZV immunity. For instance, the Brisson model included a waning of immunity rate of 0.01 for second dose vaccination in the base case while our ABM assumed a waning of zero for this group [9]. Second, our model utilized a distance-based contact network which allowed for realistic spread of infection through a population. Mediating contacts through a network may have limited the size of the chickenpox outbreaks, and consequently provides a fundamental explanation for why our model did not predict a large outbreak of chickenpox soon after vaccine implementation, but instead predicted small and episodic outbreaks. Third, because our work took place after the implementation of the second dose of the chickenpox vaccine in Canada we were able to build on Brisson's analysis to compare chickenpox vaccine schedules currently being used in various provinces [27]. Fourth, using an ABM, the disease and vaccination patterns in the population were emergent based on the individual characteristics of the agents. For instance, each agent had risk of transmission based on their type of infection (i.e. normal, breakthrough and shingles cases), a risk of infection based on their disease state and their contacts, and a likelihood of vaccination dependent on their vaccination attitude.

Our model consistently predicted a smaller decrease in chickenpox incidence for schedule SDI vaccination (12 months and 18 months), in comparison to schedule LDI (12 months and 4-6 years) (100% of paired model runs). Recent research in both Canada [13] and Europe [28] show that chickenpox incidence is highest in the under 5 age group. Since the second dose of schedule SDI happens much earlier than schedule LDI it mitigates the negative effects of primary vaccine failure and ensures more children are protected during this high-risk age. Therefore, we postulate the overall benefit of schedule SDI is based on its ability to prevent more chickenpox cases, both breakthrough and normal, before age five, which is consistent with our findings that schedule SDI has an older average age of infection than schedule LDI. Interestingly, we found even with a significantly higher waning of vaccine immunity rate and when more individuals identify as vaccine 'rejectors' (lower vaccine coverage) schedule SDI prevented a higher number of chickenpox cases than schedule LDI. Our findings are consistent with a recent modelling study done in Italy which looked at how altering chickenpox vaccination factors affect overall disease burden [29]. Using a dynamic transmission model Holl et al. [29] showed that shorter dosing intervals (5 months) are preferable to longer dosing intervals (5 years), because it limits the number of breakthrough cases of people experiencing primary vaccine failure. In comparison, when Brisson et al. [27] compared effects of providing a second dose of varicella at three different time points, an infant program (1^{st} and 2^{nd} doses- 1 year), pre-school program (1^{st} dose- 1 year, 2^{nd} dose- 5 years) and grade 4 (1^{st} dose- 1 year, 2^{nd} dose- 9 years), he found the longest time difference between doses (i.e. a grade 4 vaccine) would lead to the largest decrease in chickenpox cases. The main benefit of the grade 4 vaccination was that it significantly reduced the size of the large initial outbreak predicted by the Brisson model but not observed in our model or empirical data [13,19,27,30]. Furthermore, Brisson et al. [27] found that the effectiveness of different timings for the second dose of chickenpox vaccination was largely dependent on mixing and vaccine effectiveness assumptions, including the waning of chickenpox vaccine immunity in older age groups, two elements we have updated in our ABM.

Most chickenpox vaccine literature suggests that while there is a relatively high rate of primary vaccine failure but there is limited evidence of waning of immunity [9,17]. One exception is Chaves et al. [10] who reported an increased incidence of varicella among vaccinated persons with time since vaccination with a single dose; however, Gershon et al. [17] and Chaves et al. [10] postulate that primary vaccine failure may partially contribute to an

increase in cases over time. Using literature estimates for primary and secondary vaccine failure, Bonanni et al. [16] concluded that a shorter time interval between the two doses may reduce breakthrough varicella. Again, these findings are consistent with our model which showed a breakthrough rate that was 62% lower in schedule SDI than in schedule LDI, even 75 years post-implementation. This finding suggests with the current model assumptions, primary vaccine failure is having a greater impact on normal and breakthrough chickenpox disease rates than waning of immunity.

It is important to note that, because of the short amount of time since chickenpox vaccine introduction, we may find that the waning of immunity has a bigger impact on chickenpox infections in the future. In the past, other vaccines initially demonstrated high efficacy, but that efficacy decreased dramatically over time. The best example of this is the acellular pertussis vaccine, where there was a significant initial decline in cases, but the incidence of pertussis slowly started to increase as an individuals' immunity to the vaccine waned. Our sensitivity analysis showed that while a lower waning of immunity had a negligible impact on disease outcomes, when we assumed a higher waning of immunity rate we saw significantly more chickenpox and breakthrough cases 75 post-vaccine introduction. However, even at this high waning of immunity rate we still saw a significant decrease in chickenpox cases with chickenpox vaccination.

While our model found evidence that schedule SDI could lead to a greater reduction in the incidence of chickenpox as compared to schedule LDI (100% of paired runs finding lower chickenpox incidence in schedule SDI), these results are not conclusive, particularly as the 95% predictive intervals overlapped. Therefore, it is important policy-makers consider other factors when determining the appropriate schedule for the chickenpox vaccination. For instance, if chickenpox is provided in a combination MMRV vaccine, then policymakers should also consider how the timing of the dose may impact the other antigens in the vaccine [31]. In fact, Perez et al. [31] found a decreasing pattern in the proportion of individuals who were seronegative to measles when the first dose of the measles-containing vaccine was given at 11, 12, 13-4 and 15-22 months. Another element to consider is the safety profile of the vaccines, specifically if the risk of adverse events changes with vaccine schedule. For instance, MacDonald et al. [5] found an increased risk of febrile seizures in individuals who received first dose MMRV vaccine compared to those who received MMR and V separately. Moreover,

coverage rates may also change with different vaccination schedules, with combination vaccines in general, and MMRV in particular, associated with a significantly higher coverage rate than other vaccine alternatives (e.g. MMR) [32,33]. While our sensitivity analyses showed that higher coverage rates only have a minor impact on overall chickenpox incidence, lowering coverage rates by approximately 10% could lead to significantly more chickenpox cases in both schedules, and therefore it may be an important consideration when implementing a vaccine program.

While this study was to our knowledge the first to explore the differential impact of chickenpox vaccine strategies using an ABM, it had some notable limitations. First, we were only able to run our model on a population of 500,000 people and over 30 paired runs. A larger number of runs could result in smaller predictive intervals and therefore a more accurate picture of the relative effectiveness of different chickenpox vaccination schedules. However, as stated in Chapter 4, we saw very little deviation in our model when we ran it on both smaller and larger populations suggesting a robustness of results to broad population ranges. Second, due to the complexity of the chickenpox vaccination schedules across Canada we were only able to test a few of the different schedules and their impact on certain outcomes in this analysis. In the future we hope to explore these questions in more detail using this ABM. Third, while we used a distance-based contact network to account for disease transmission in our model, we were not able to completely replicate a realistic age-dependant contact matrix. Researchers are currently building these realistic networks through empirical studies of individuals and their contacts in Canada [34]. When these networks become more available we hope to apply them to our model.

As the two vaccination strategies outlined in this study may lead to diverse costs and effects, prior to making decisions about the relative benefits of the schedule, it is important future research test the cost-effectiveness of various chickenpox vaccination schedules. This study and our ABM provide the foundation for analysing a more complex set of potential schedules and their impact on a wider set of outcomes.

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CHAPTER 6- THE COST-EFFECTIVENESS OF CHICKENPOX VACCINATION IN ALBERTA, INCLUDING AN ANALYSIS OF DIFFERENT SCHEDULES

My contributions to this manuscript included conceptualizing the model updates, conceiving and designing the study, helping debug model issues, running the experiments, analysing and interpreting the findings and manuscript preparation. Wade McDonald, updated the previous model to measure the costs and effects (QALY) associated with chickenpox disease and vaccination, added to the results outputted from the model, helped debug issues related to model output (e.g. issues measuring QALY) and oversaw the running of the model experiments. Dr. Nathaniel Osgood aided in the conception and the design the study and oversaw all model adaptations and model runs. Dr. Marwa Farag, Dr. Wu Zeng, Dr. Alexander Doroshenko aided in the conception and design of the study, and the interpretation and analysis of the findings.

Following our findings in **Chapter 5** that chickenpox vaccine significantly reduces disease incidence over time; as well as our discovery of the differential effectiveness of two different vaccination schedules, the next step of our analysis was to determine the cost-effectiveness of chickenpox vaccination overall and for different vaccination schedules. Based on our findings in **Chapter 4** we were also able to include the impact of chickenpox vaccination on shingles incidence in our cost-effectiveness analysis. In this chapter, we discuss how we updated the agent-based model developed in previous chapters to calculate the costs and QALYs associated with certain events (e.g. doctor visits, hospitalizations, vaccination). As the ABM was already calibrated to Alberta empirical data on chickenpox and shingles both before and after the implementation of the chickenpox vaccination, as well designed to test the impact of chickenpox vaccination on chickenpox and shingles disease outcomes, it was well placed to evaluate the cost-effectiveness of chickenpox vaccination. Therefore, we tested the overall cost-effectiveness of chickenpox vaccine in Alberta for both the schedule with a long dosing interval and a short dosing interval, as well as the cost-effectiveness between the two schedules.

6.1. Introduction

Chickenpox is generally considered a mild, self-limiting childhood disease; however severe complications can occur which can lead to expensive hospitalization and death [1]. To reduce the impact of the disease and its complications a chickenpox vaccine was develop in the 1970s [2], and since its development it has been included as part of the routine childhood vaccination studies in many countries, including Canada and the United States [3,4]. Although many factors contribute to a country's decision to implement the chickenpox vaccine in their routine immunization schedule, the chickenpox and vaccine-associated costs, its impact on quality of life and the overall cost-effectiveness of the vaccine are often key considerations [3,5,6].

Systematic reviews of economic evaluations of the chickenpox vaccination demonstrate that vaccination in high-risk groups and routine childhood vaccination are cost-saving from a societal perspective (i.e. both health care and indirect costs) [7,8]. However, the cost-effectiveness of the vaccine from the healthcare perspective (i.e. costs of chickenpox to the health care system) is more uncertain, with studies from around the globe predicting cost-effectiveness ratios in the range of $11,900 to $99,300 per life-year gained [8,9]. The infectious disease models that estimated the cost-effectiveness of a universal chickenpox vaccination in Canada, found similar results to these reviews, as vaccination was cost-saving when considering indirect costs but generally cost-ineffective from the healthcare perspective [10,11].

The two Canadian universal chickenpox vaccine economic evaluations were conducted prior to the implementation of the vaccine in the population (ex-ante), and therefore provided useful information to policy-makers deciding whether to include the chickenpox vaccine in provincial vaccine schedules. However, as we noted in **Chapter 2**, economic evaluations conducted pre-vaccine implementation, need to make assumptions about unknown parameter values such as, attainable coverage levels, the cost of the chickenpox vaccine and its real-world effectiveness. A review of economic evaluations of chickenpox by Thiry et al. [9] suggested that future economic evaluations of chickenpox would benefit from more accurate data on the effectiveness of the chickenpox vaccine, including the possibility of waning of immunity and the impact on shingles incidence [7,9]. An update of these economic evaluation would not only provide policy-makers with a more pertinent estimate of the cost-effectiveness of chickenpox but also an idea of the accuracy of economic evaluations done prior to vaccine licensing and

implementation. Furthermore, ex-post (i.e. post-implementation) economic evaluation provide researchers the opportunity to answer policy-questions that become pertinent following the implementation of the vaccine.

Thiry et al. [9] further noted that to date many economic evaluations of chickenpox use static models, and that future research should prioritize the use of dynamic models that can capture the indirect effects of vaccination. In fact, dynamic models are particularly important to measuring the cost-effectiveness of the chickenpox vaccine, as they can highlight important externalities and dynamic elements of vaccination, like boosting and waning of natural and vaccine immunity, as well as herd immunity. Furthermore, dynamic models are generally more sensitive to changes in vaccine parameters, such as vaccine coverage and effectiveness [7,9]. Guidelines for economic evaluation, including those released by WHO [12] and the Canadian Agency for Drugs and Technologies in Health [13] recommend cost-effectiveness studies have the capacity to measure the indirect effects and costs associated with vaccinations. Agent-based models (ABM) are uniquely placed to measure the cost-effectiveness of preventive infectious diseases interventions, especially one as complicated as the chickenpox vaccination, as they can recreate realistic disease dynamics (e.g. contact-based transmission, small and episodic chickenpox outbreaks). Furthermore, in agent-based modelling the population-level cost and quality adjusted life-years (QALYs) estimates naturally emerge from the costs and QALYs captured for each individual in the model, much like real-life. Furthermore, ABMs can capture the costs and QALY of a wide range of disease, vaccination and healthcare utilization outcomes.

Although previous economic evaluations found that chickenpox vaccination may be cost-effective under certain circumstances, there remains a lot of unknowns surrounding the costs and effects of this relatively new vaccine. One reason some countries have resisted implementing the chickenpox vaccine is the concern that vaccination could limit natural boosting of varicella zoster virus (VZV) immunity, which some studies suggest will increase shingles incidence [14–16]. While most chickenpox economic evaluations show that chickenpox vaccine is likely cost-effective or cost-saving from the societal perspective, this changes dramatically if the chickenpox vaccine leads to an increase in shingles cases [11,17]. In **Chapter 4** we demonstrated that chickenpox vaccination may have a relatively small impact on shingles outcomes, under the reasonable assumption of a short duration of VZV boosting. [16,18,19]. Furthermore, we illustrated an ultimate decrease in shingles cases over time, due to the lower risk of developing

shingles with vaccine-strain VZV. These factors may influence the overall cost-effectiveness of the chickenpox vaccine.

Policy-makers continue to debate the most cost-effective schedule for the chickenpox vaccines, including the number of doses, the use of combination vaccines, and the appropriate timing for vaccine delivery. The question of the cost-effectiveness of the different chickenpox vaccine schedules remains unanswered in the literature. The cost-effectiveness of different chickenpox vaccine schedules could be altered by several factors. Specifically, reduction in cases, as well as shifts in the type and age of chickenpox infection with different schedules may impact both costs and QALY. For example, breakthrough cases of chickenpox are generally not as severe, and therefore on average these cases are less costly and have a smaller impact on QALYs lost than normal cases of chickenpox. In comparison, a shift in chickenpox to older age groups will lead to more severe and costly cases of the disease [2,14,17].

Based on these defined gaps in literature we aimed to test the cost-effectiveness of the chickenpox vaccine in Alberta, Canada, by inputting updated data on the costs, utilities, health utilization probabilities associated with chickenpox disease and vaccination into a complex ABM of chickenpox and shingles transmission, disease outcomes and vaccination. Furthermore, using our ABM we aimed to compare the cost-effectiveness of the chickenpox vaccine under two diverse schedules, as well as the cost-effectiveness between schedules, to measure if dose timing has an impact on cost-effectiveness.

6.2. Methods

6.2.1. Economic evaluation methods

We conducted a cost-utility analysis using the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines for economic evaluations [13]. We undertook both a publicly-funded healthcare payer and a societal perspective to fully capture the costs and effects of chickenpox vaccination. The healthcare perspective provides policy-makers estimates of the direct costs associated with chickenpox vaccination and is particularly relevant to health care budgeting. However, as chickenpox and shingles are both diseases that are shown to reduce productivity and garner significant personal costs per case, it was also imperative to conduct the cost-effectiveness analysis from the societal perspective [20–22]. Furthermore, considering the cost-effectiveness from both perspectives will allow for greater comparability with previous and future Canadian cost-effectiveness of chickenpox vaccination studies [10,11]. However, there

may be decision-making challenges, including for resource allocation, if the societal and healthcare perspective have different findings.

Our target population was children aged 12 months to 4-6 years who are eligible to receive the chickenpox vaccine in Alberta. Our model was previously fit to Alberta data before the implementation of chickenpox vaccination (**Chapter 4**) and checked for consistency with data post-vaccination (**Chapter 5**). We applied two different vaccine schedules used by a variety of Canadian provinces, to test how schedule can impact the cost-effectiveness of the chickenpox vaccine. We discounted both costs and QALYs at a rate of 1.5% [13]. Discounting is the process by which we adjust future costs and benefits to present value; in this case costs and QALYs accrued one year after the start of vaccination are valued 1.5% less than costs and QALYs accrued within the first year of vaccination. Furthermore, we used a long time-horizon of 75 years to ensure we could capture all the costs and outcomes associated with chickenpox vaccination.

6.2.2. Model description and parameterization

Full descriptions of the ABM we used in this analysis are available in **Chapter 4** and **Chapter 5**. In these two chapters we describe how the model represents chickenpox and shingles disease transmission and acquisition, and chickenpox vaccine implementation, as well as the parameters used to populate the original model. Furthermore, we explain how we calibrated the model to empirical data both before (**Chapter 4**) and after (**Chapter 5**) chickenpox vaccine. Below we describe the updates we made to the chickenpox and shingles ABM to conduct an economic evaluation analysis. The data-inputs required to conduct the cost-effectiveness analysis (i.e. health care utilization probabilities, costs and quality of life parameters) are presented in **Table 6.1** and **Table 6.2**. A complete outline of the parameters we used in the model is available in **Appendix G.**

Table 6.1. Probabilities of health utilization in ABM

ABM parameter name	Parameter description	Parameter estimates	Reference
probGPVisitCP	Percent of total chickenpox cases that will visit a GP on infection	40%	Kwong et al. [23]; Lieu et al., [24]; Bilcke et al. [25]
tfFracHospitalizedCPbyAge	Percent of chickenpox cases that go to the hospital by age group.	0-1 years= 1.8%; 2-4 years= 0.4%; 5-11 years= 0.2%; 12-18 years= 0.4%; 19-24 years= 0.5%; 25-44 years= 1.4%; 45-65 years = 1.9%; 65+ years= 7%	Brisson et al. [26]
tfLOSHospitalizedbyAge	Length of stay in days that a chickenpox case stays in hospital by age.	<1 years = 2.92 days; 1-4 = 3.23 days; 5-9 years= 4.30 days; 10-14 years = 5.13 days; 15-19 years = 8.86 days; 20+ years = 5.70 days	Nowgesic et al. [27]; Law et al [28]
probEDVisitCP	Percent of chickenpox cases that go to the emergency room	0.035	Kwong et al. [23]
probEDVisitShingle	The percent of shingles cases that of shingles cases that visit a GP. The rates we calibrated shingles incidence to are for medically attended shingles and so we assumed everyone would go to the GP.	1.0	Russell et al [29]; Brisson et al. [26]; Edgar et al. [30]
tfFracHospitalizedShinglebyAge	Probability of a shingles cases being hospitalized by aged group.	0-4 years = 0.0055; 5-14 years= 0.0035; 15-44 years = 0.0028; 45-64 years = 0.007; 65+ years= 0.0265	Brisson et al. [26] confirmed by Tanuseputro et al. [31] and updated to current day using Friesen et al. [21]
tfLOSHospitalizedShinglebyAge	Average length of stay in the hospital for a shingles case by age group	0-4 years= 5.1 days; 5-14 years= 4.6 days; 15-44 years= 8 days; 45-64 years= 11.6 days; 65+ years= 20 days	Brisson et al. (2001)- [26]
tableFunctionChanceOfPHNByAge	Percent of shingles patients who develop PHN by age. PHN is defined here as clinically relevant pain for >90 days.	0-48 years= 5%; 49-60 years= 14.6%; 61-70 years= 20.5%; 70+ years= 33.8%	Dolet et al. (2010) [32] with assumption for the 0-48 group based on Friesen et al. 2017[21]
CustomDistributionPHNDuration	The average length in days of a case of PHN. number of days a case for a case of PHN.	90-120 days= 25%; 120-244 days= 50%; 244-700 days= 25%	Drolet et al. (2010) [32]and Kawai et al. (2014) [33]

Table 6.2. Cost and utility parameter values

Parameter (ABM name)	Description	Estimate[1]	Reference
Direct costs			
costGPVisitCP	Average cost per chickenpox case that goes to a GP in Canada.	$40.96	Alberta Health [34]
costPerDayHospitalizedCP	Cost per hospitalization for chickenpox per day.	$1,523	Law et al. [28]; Nowgesic et al. [27]
costEDVisitCP	Cost per emergency room visit for a chickenpox case.	$139	Dawson et al. [35]; Alberta Health [34]
costPerPrescriptionMedCP	Cost per prescription medication (government paid) for chickenpox. Public spending as a percentage of total prescription med spending in Alberta= 42.5%	Government costs= $0.75	Law et al. [20]; Canadian Institute for Health Information [36]; Alberta Health [34]
costPersonalExpenseCP	Personal out of pocket expenses to care for a chickenpox case by age group. Costs include, over-the-counter and prescription medication, travel and gifts.	costPersonalExpense CPUnder4= $105.60 costPersonalExpense CPOver4= $43.84	Law et al. [20]
costGPVisitShingle	GP costs for each shingles episode, and therefore can include multiple visits to the doctor.	$84.95 per shingles episode	Friesen et al. [21]
costPerDayHospitalizedShingle	Cost per day hospitalized for shingles.	$929.81 per day	Friesen et al. [21]
costPerPrescriptionMedShingle	Cost for prescription medications (government paid) per shingles episode. Public spending as a percentage of total prescription med spending in Alberta= 42.5%	$58.31	Friesen et al. 2017 [21]; Canadian Institute for Health Information [36]
costPersonalExpenseShingle	Personal expense costs per shingles case. Includes prescription and over-the-counter medication as well as travel costs.	$84.86	Oster et al. [37], Rafferty et al. [38]; Friesen et al. [21]; Canadian Institute for Health Information [36]
Indirect costs			
costProductivityLossCP[2]	Cost per case of chickenpox for lost productivity, all ages, includes time taken off work and leisure, and money spent paying for caregiving.	$280.84 per case	De Wals [39]
costProductivityLossHospitalized	Productivity losses per day from being in hospital. These costs are the number of hours lost from being in hospital or taking care of your child in hospital multiplied by the average wage in Canada.	$224.10 per day	De Wals [39]; Statistics Canada [40]
costProductivityLossShinglesOver50	Cost per case of shingles for lost productivity, for individuals 50 years and over with no PHN.	$345.41 per case	Drolet et al. [22]; Statistics Canada [40]

costProductivityLossShinglesUnder50	Cost per case of shingles for lost productivity, for individual under 50 years of age with no PHN.	$666.44 per case	Drolet et al. [22]; Statistics Canada [40]; Trading Economics [41]
costProductivityLossPHNOver50	Cost per PHN case of shingles for lost productivity in individuals over 50 years of age.	891.98 per case	Drolet et al. [22]
costProductivityLossPHNUnder50	Cost per PHN case of shingles for lost productivity in individuals under 50 years of age.	$1,720.99 per case	Drolet et al. [22]; Statistics Canada [40]; Trading Economics [41]
costProductivityLossHospitalizedShinglesOver50	Cost per hospitalized case of shingles per day for lost productivity in individuals over 50.	$76.19 per day	Brisson et al. [26]; Statistics Canada [40]; Trading Economics [41]
costProductivityLossHospitalizedShinglesUnder50	Cost per hospitalized case of shingles per day for lost productivity in individuals under 50.	$147.01 per day	Brisson et al. [26]; Statistics Canada [40]; Trading Economics [41]
Vaccination and intervention costs			
CostCPVacc	Cost to vaccinate a child with the varicella, using the MMRV vaccine within Alberta public health clinics. Including procurement costs, labour costs and supply costs.	CostCPVaccDose1= $55.22 CostCPVaccDose2= $55.22	Institute Health Economics [42]; Mercer [43]; Personal Communication
costFebrileSeizures	The cost to treat a febrile seizure in the emergency room.	$139	Dawson et al. [35]
Quality of life			
qualityOfLifeBase	Utility weight for individuals with no pain, i.e. baseline.	0.855	Van Hoek et al. [44]
qualityOfLifeCPUnder15	Utility weight for individuals under 15 who get a regular case of chickenpox	0.76	Brisson & Edmunds [45]; supported by Hoek et al. [46]; Bilcke et al. [25]; Merrett et al. [47]
qualityOfLifeCPOver15	Utility weight for individuals over 15 who get a regular case of chickenpox, similar to a mild case of shingles.	0.67	Van Hoek et al. [46] supported by Drolet et al. [22]
qualityOfLifeWeakUnder50	Utility weight for individuals under 50 who get a breakthrough case of chickenpox.	0.83	Van Hoek et al. [46]
qualityOfLifeWeakOver50	Utility weight for individuals 50 and over who get a breakthrough case of chickenpox.	0.76	Van Hoek et al. [46]
qualityOfLifeHospitalizedCP	Utility weight for individuals who are hospitalized for chickenpox.	0.36	Merrett et al. [47]
qualityOfLifeShingles	Utility weight for individuals who get a normal case of shingles.	0.59	Drolet et al. [32] supported by Brisson et al. [48] and Wijck et al. [49]
qualityOfLifePHN	Utility weight for individuals who get PHN from shingles	0.67	Drolet et al. [32]; supported by Brisson et al. [48]
qualityOfLifeHospitalizedShingle	Utility weight for individuals who are hospitalized from shingles.	0.32	Van Hoek et al. [44]

[1]All costs are presented in 2017 Can$ and were adjusted using the Canadian consumer price index [50].

[2]Productivity costs include both time off work and caregiver time.

The first update to the model was to add in health utilization probabilities. Based on certain disease and vaccination events we added in probabilities of going to a physician or emergency room, being hospitalized, having a vaccine adverse event and having a disease complication that lead to death. Therefore, individuals who entered the 'infectedCP' state had a certain probability of visiting a physician (*probGPVisitCP*) or the emergency room (*probEDVisitCP*), as well as being hospitalized (*tfFracHospitalizedCPbyAge*) and dying from a complication (*probabilityOfComplicationDeathCP*). For 'infectedWeaklyCP' we included a probability of a physician visit (*probGPVisitCPWeak*); however, there was no risk of an emergency room visit, hospitalization or death from this state.

Similarly, individuals who were in the 'infectedShingles' state had a certain probability of death from shingles (*probabilityOfComplicationDeathShingle*), probability of post-herpetic neuralgia (PHN) based on age (*tableFunctionChanceOfPHNByAge*) and probability of hospitalization based on age (*tfFracHospitalizedShinglesByAge*). If an agent was hospitalized for shingles or chickenpox they transitioned from the 'home' state in the statechartTreatment to the 'inHospital' state, where their length of stay was dependent on their age (*tfLOSHospitalizedCPbyAge* and *tfLOSHospitalizedShinglebyAge*). Finally, there was a *probFebrileSeizure* associated with entering the Protected1 state following the receipt of 1st dose vaccination to account for vaccine adverse events.

To conduct the analysis from both the healthcare and societal perspectives, we included direct health care costs, personal costs and productivity loss, which were represented in the model either as episodic costs (i.e. single costs triggered by a certain event) or state-based cost (i.e. added up each day an agent remained in a state). All costs are presented in 2017 Can$, and were adjusted for inflation using the Canadian consumer price index [50].The direct medical costs to the health care system were mainly episodic costs that depended on the health care utilization probabilities described above, and included physician (*costGPVisitCP*; *costGPVisitShingles*), emergency room visit (*costEDVisitCP*; *costEDVisitShingle*), as well as the medication costs provided through the Government of Alberta for each chickenpox and shingles case (*costPerPrescriptionMedCP*; *costPerPrescriptionMedShingle*). Hospitalization costs were included as a state-based cost that was triggered every day an individual remained in the 'inHospital' state (*costPerDayHospitalizedCP*; *costPerDayHospitalizedShingle*). We also included the cost of chickenpox vaccination as an episodic cost when an individual receives

either 1st or 2nd dose vaccination (*costCPVaccDose1*; *costCPVaccDose2*). Costs included as part of vaccination costs were procurement costs, as well as labour, administration and supply costs. Finally, we included a cost for febrile seizures from 1st dose vaccination (*costFebrileSeizure*).

Personal costs included over-the-counter medication, travel and personal prescription medication costs. These costs were largely episodic, partially based on age and occurred when someone entered either the 'infectedCP' state (*costPersonalExpenseCPUnder4*; *costPersonalExpenseCPOver4*) or the 'infectedShingle' state (*costPersonalExpenseShingle*). Finally, we considered productivity losses, which were calculated in the disease and treatment statecharts, including different productivity losses for each of these states: 'infectedCP' (*costProductivityLossCP*), 'inHospital' for chickenpox (*costProductivityLossHospitalizedCP),* 'infectedShingle' (*getCostProductivityLossShingleByAge*), 'PHN' (*getCostProductivityLossPHNByAge*) and 'inHospital' for shingles (*costPerDayHospitalizedShingle*). These productivity losses included both the time spent taking care of the chickenpox case and any cost accrued for caregiving. The productivity costs for 'infectedShingle', 'PHN' and 'inHospital' for shingles, partially depended on age. While deaths associated with chickenpox were captured in our model, we did not estimate their associated productivity loss, as the mortality rates were very low (<1 death per 500,000 person-years).

Similarly to productivity loss, each agent had a quality of life (QoL) that depended on their disease and treatment state, as well as their age. QoL is calculated on a per day basis for each model agent (**See Table 6.2**). We included a base quality of life (*qualityOfLifeBase*) for any individual not in a disease state that impact their quality of life. Treatment states that impact quality of life included: 'infectedCP' (*qualityOfLifeCPUnder15; qualityOfLifeCPOver15*), 'weaklyInfectedCP' (*qualityOfLifeWeakUnder50, qualityOfLifeWeakOver50),* 'inHospital' for chickenpox (*qualityOfLifeHospitalizedCP),* 'infectedShingle' (*qualityOfLifeShingles*), 'PHN' (*qualityOfLifePHN*) and 'inHospital' for shingles (*qualityOfLifeHospitalizedShingle*). QoL estimates for a standard chickenpox [45] and shingles [32] case were based on primary quality of life studies, specifically the standard gamble and the Health Utilities Index mark 2 (HUI2) questionnaire for chickenpox, and the EuroQoL EQ-5D for shingles. The individuals QoL per day (depending on their current state) are then added up over the entire year and population to determine total QALYs per year in the population. Durations for QALYs were based on the time

spent in disease states (see **Appendix G**); for instance, *durationCP* determined the amount of time an individual had a chickenpox QoL.

6.2.3. Main experiment

In our main analysis we ran the model for 175 years. The first 100 years were to initialize the model (as described in **Chapter 4**), with costs and effects being measured over the last 75 years. We include three comparators in our main analysis:

- No vaccination: Disease outcomes, costs and QALYs were calculated for 75 years (year 100-175) with no introduction of vaccination.
- Schedule with long dosing interval (schedule LDI): Disease and vaccination outcomes, costs and QALYs were measured for 75 years (year 100-175) following introduction of vaccination at year 100, with children receiving 1st dose chickenpox vaccination at 12 months and 2nd dose vaccination between 4 and 6 years.
- Schedule with short dosing interval (schedule SDI): Disease and vaccination outcomes, costs and QALYs were measured for 75 years (year 100-175) following introduction of vaccination at year 100 with children receiving 1st dose chickenpox vaccination at 12 months and 2nd dose vaccination at 18 months.

We ran each comparator twice, once considering the impact of shingles on the overall costs and QALYs, and once ignoring the overall shingles impact. All other variables remained consistent across all three scenarios.

The population size, total discounted costs and discounted QALYS for the 75 years following vaccination were summed for each run. All costs and QALYS are presented in medians per capita [95% predictive interval] across all simulation results. 95% predictive intervals represent the 2.5th and 97.5th percentiles from the sample of model runs. The costs and QALYs were presented per capita to account for differences in population size between model runs. For all model run sets (i.e. no vaccination, schedule LDI and schedule SDI) we conducted at least 30 paired runs. Pairing the model runs ensured that one set of runs for baseline, schedule LDI, and schedule SDI started with the same values for the transition probabilities, health utilization probabilities, as well as the cost and utility parameters and variables. Based on the previous sample size calculation describe in **Chapter 4**, and practical considerations (i.e. model run time) we decided to maintain our sample size at 30 runs minimum (90 non-paired runs). Running the model multiple times meant we could account for some of the stochastics in agent-

based modelling and calculate an incremental cost utility ratio (ICUR) for each run, providing both a range of outcomes for cost-effectiveness, as well as a point estimate.

6.2.4. Sensitivity analysis

Using scenario analysis, we varied duration of boosting, discount rate for benefits, vaccination attitude, primary vaccine failure and secondary vaccine failure to see their relative impact on the cost-effectiveness of different chickenpox vaccine schedules. We tested the impact of a shorter duration of VZV boosting (duration of boosting= 2 years; waning of immunity coefficient= 0.5), as identified in **Chapter 4**, to observe its impact the cost-effectiveness of chickenpox vaccination. By shifting 15% of hesitant individuals to vaccine acceptors and then shifting 15% of hesitant individuals to vaccine rejectors, we tested the effects of higher and lower vaccination coverage. Furthermore, we used ranges in the literature to vary primary vaccine failure for first dose vaccine between 9% to 24%, while simultaneously varying the primary vaccine failure for second dose between 5% and 16% [2,51–54]. As the rate of secondary vaccine failure remains largely unknown we considered a wide range, between 0 and 5%, in our sensitivity analysis. We also conducted a sensitivity analysis on one of our main economic evaluation assumptions, specifically the discount rate for the benefits, which we tested at 0%.

6.3. Results

6.3.1. Main experiment results

Similar to our findings in **Chapter 5**, we discovered chickenpox vaccination lead to a significant decrease in chickenpox incidence. Furthermore, we found the 95% predictive intervals for chickenpox incidence overlapped between schedule SDI and schedule LDI; however, 100% of the paired runs found that schedule SDI had a lower chickenpox incidence rate than schedule LDI (**Table 6.3**). The decreased risk of chickenpox with vaccination contributed to a lower rate of chickenpox hospitalizations, as well as an increase in shingles cases, consistent with **Chapter 4**. From the healthcare perspective we found that both chickenpox vaccination strategies were more expensive than no vaccination, both when we considered and ignored the impact on shingles. Specifically, vaccination cost on average $0.47 more per person-year than no vaccination when considering shingles, and $0.28 more per person-year when not considering shingles. However, chickenpox vaccination resulted in notable

savings in comparison to no vaccination from the societal perspective, reducing cost by an average of $1.83 per person-year with shingles and $2.15 per person-year without shingles (**Table 6.3**). While schedule SDI was slightly cheaper than schedule LDI from the societal perspective, and more expensive from the healthcare perspective, the 95% predictive intervals for schedule SDI and LDI for these values overlapped, suggesting there was no significant difference.

Table 6.3. Disease, healthcare, cost and QALY outcomes over 75 years post chickenpox vaccination (median and 95% predictive interval across 30 model runs).

	Scenario (75 years post-vaccination)		
	No vaccine	**Schedule LDI[2]**	**Schedule SDI[2]**
Chickenpox incidence (per 1,000 person-years)	12.11 (12.0, 12.26)	0.61 (0.50, 0.74)	0.49 (0.39, 0.64)
Breakthrough (% of total cases)	-	17.92% (14.55, 21.06)	14.96% (11.13, 18.26)
CP Hospitalization per capita (per 100,000 person-years)	6.09 (5.89, 6.27)	0.48 (0.39, 0.58)	0.39 (0.35, 0.48)
Healthcare costs ($ per capita)[1]	$1.40 (1.40, 1.41)	$1.86 (1.84,1.90)	$1.88 (1.86, 1.92)
Societal costs ($ per person year)	$5.65 (5.58, 5.72)	$3.82 (3.76,3.92)	$3.82 (3.75, 3.91)
QALY[3] (per 1,000,000 person-years)	854,748.42 (854,745.63, 854,750.08)	854,746.99 (854,744.89, 854,748.33)	854,746.85 (854,745.85, 854,748.58)
Healthcare costs- no shingles[4] ($ per person-years)	$0.42 (0.41, 0.44)	$0.69 (0.69, 0.71)	$0.71 (0.71,0.72)
Societal costs- no shingles ($ per person-years)	$3.00 (2.93, 3.07)	$0.85 (0.79,0.92)	$0.84 (0.84, 0.86)
QALY- no shingles (per 1,000,000 person-years)	854,965.79 (854,965.05, 854,966.44)	854,997.73 (854,996.91, 854,998.35)	854,998.07 (854,997.13, 854,998.61)

[1]All costs and QALYs were discounted at a rate of 1.5%

[2]Schedule LDI is 1st dose MMRV at 12 months and 2nd dose at 4-6 years, and Schedule SDI is first dose of MMRV at 12 months and second dose at 18 months.

[3]We represent QALY in person-years to account for differences in population size between model runs.

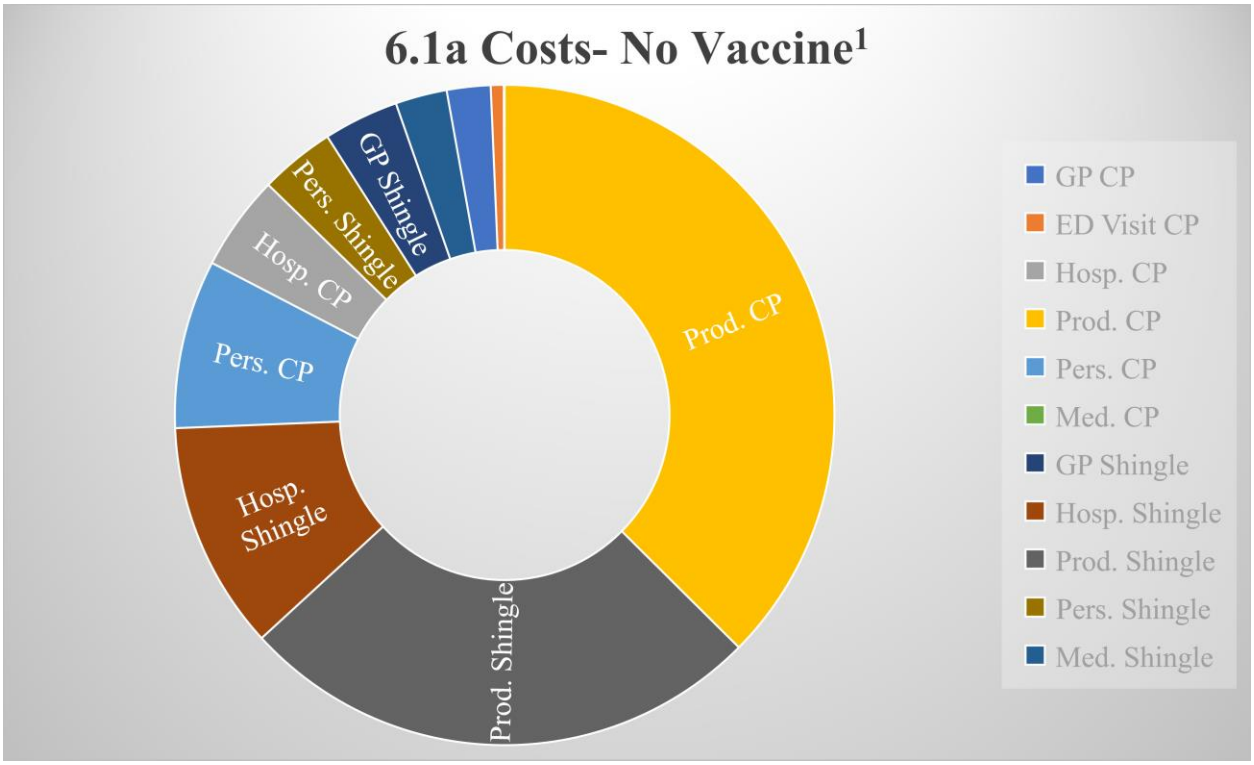
[4]No shingles runs assumed there was no cost or loss of QALY associated shingles, therefore the differences between baseline, schedule LDI and schedule SDI were only based on differences in chickenpox incidence.

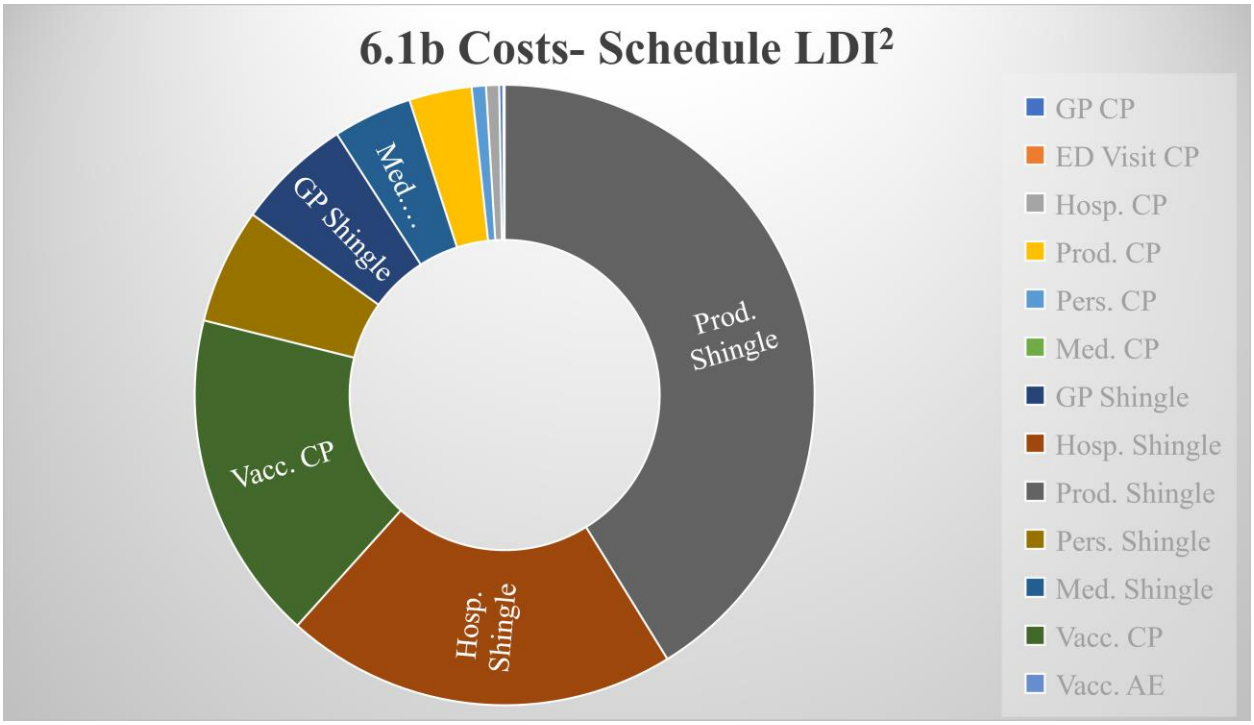
Total societal costs per year under the no vaccination scenario were approximately $2,659,741, in comparison to the vaccination scenarios, which had a cost around $1,749,674 per year (median population across all runs= 470,424). Under the no vaccination scenario indirect

costs, including productivity loss chickenpox (37%), productivity loss shingles (26%), and the personal costs for chickenpox (8.2%) and shingles (3.7%), contributed far more to the total costs than direct costs (75% versus 25%) (**Figure 6.1A**). With chickenpox vaccination, for both schedule SDI and LDI vaccination, while productivity loss from shingles contributed to a larger proportion of the total costs (41%), the percentage of total costs attributed to chickenpox, including productivity, personal and hospital costs decreased dramatically (**Figure 6.1B, Figure 6.1C**). Chickenpox vaccination had a notable impact on costs, accounting for 18% in schedule SDI and 17% in LDI of total societal costs, and costing between approximately $309,880 and $321,609 per year for a median population of 470,424 agents.

Overall, we found that when not considering the impact on shingles QALYs were significantly greater with vaccination than without vaccination, with an increase of 3 QALY per 100,000 person-years (**Table 6.3**). However, the opposite was true when we considered the impact of shingles, with QALY per person decreasing with chickenpox vaccination, most likely because of the associated rise in shingles incidence.

Ignoring the impact on shingles, we ascertained that vaccination was cost-saving from the societal perspective (**Table 6.4**) and remained cost-saving across all runs and both schedules, as shown in **Figure 6.2a**. Moreover, from the healthcare perspective, without considering shingles we found that both schedules resulted in higher costs but significant gains in QALY, and therefore found vaccination was highly cost-effective based on cost-effectiveness thresholds reported in that literature, with ICURs less than 20,000 per QALY gained [55] (**Figure 6.2b**, **Table 6.4**). However, the ICUR outcomes change when we consider the impact on shingles, in these scenarios vaccination was either dominated by the no vaccination scenario, or highly cost ineffective at $1,184,999-$1,481,433 per QALY gained. As these are just point estimates based on multiple runs it is important to consider the distribution of ICURs as presented in **Figure 6.2a** and **Figure 6.2b**. For instance, while 79% of schedule LDI and schedule SDI runs found that vaccination would not be cost-effective from the societal perspective when considering shingles, 21% of runs estimated vaccination would be cost-saving. This figure illustrates that vaccination is consistently cheaper than no vaccination from the societal perspective, but there are a range of QALY outcomes, with some showing QALY is higher with vaccination than no vaccination, and others showing contradictory results.


6.1a Costs- No Vaccine[1]
Prod. CP
Prod. Shingle
Hosp. Shingle
Pers. CP
Hosp. CP
Pers. Shingle
GP Shingle
GP CP
ED Visit CP
Hosp. CP
Prod. CP
Pers. CP
Med. CP
GP Shingle
Hosp. Shingle
Prod. Shingle
Pers. Shingle
Med. Shingle


6.1b Costs- Schedule LDI[2]
Prod. Shingle
Hosp. Shingle
Vacc. CP
GP Shingle
Med.…
GP CP
ED Visit CP
Hosp. CP
Prod. CP
Pers. CP
Med. CP
GP Shingle
Hosp. Shingle
Prod. Shingle
Pers. Shingle
Med. Shingle
Vacc. CP
Vacc. AE

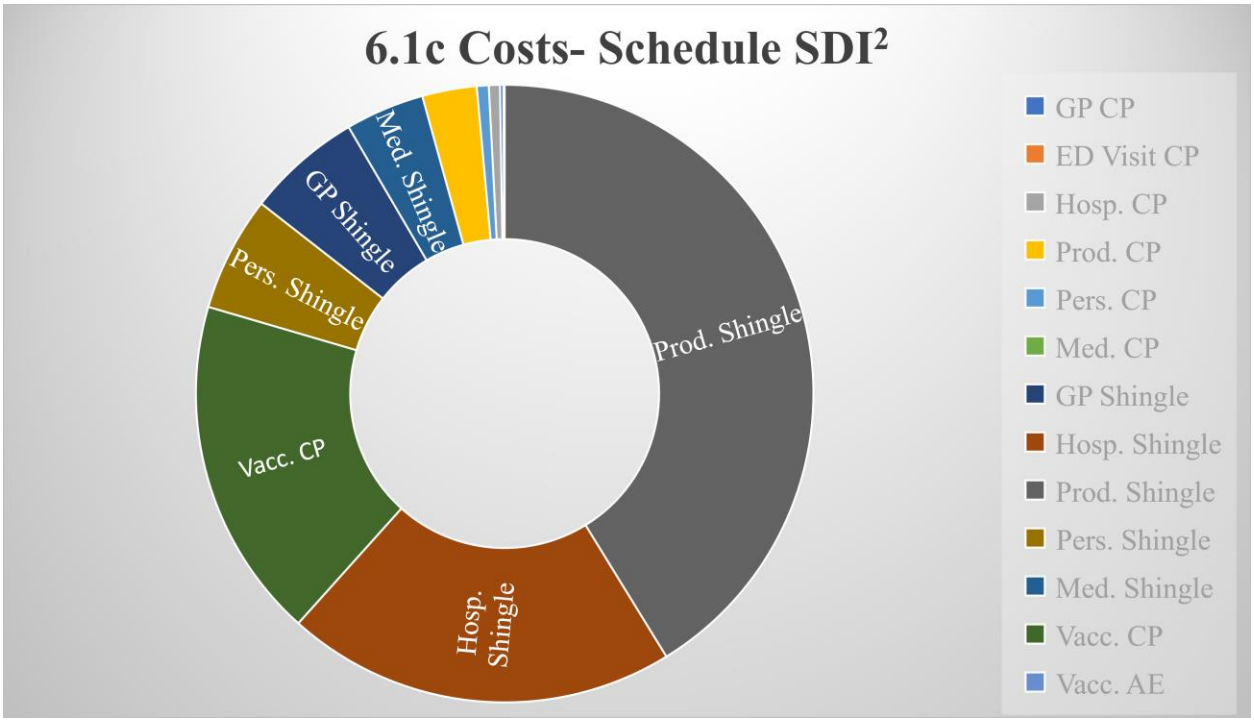


Figure 6.1. Type of costs as a percentage of the total costs, with (schedule SDI and schedule LDI) and without chickenpox vaccination.

[1]Costs displayed in all three charts include: cost of a general practitioner for chickenpox (GP CP), emergency department visit chickenpox (ED Visit CP), cost of hospitalization chickenpox (Hosp. CP), productivity loss chickenpox (Prod. CP), personal costs chickenpox (Pers CP), medication cost for chickenpox (Med CP), cost of a general practitioner for shingles (GO Shingle), cost of hospitalization shingle (Hosp. Shingle), productivity loss shingles (Prod. Shingle), personal costs shingles (Pers. Shingle), medication costs shingle (Med. Shingle), cost chickenpox vaccination (Vacc. CP) and cost of adverse events from chickenpox vaccination (Vacc. AE)
[2]Schedule LDI is 1st dose MMRV at 12 months and 2nd dose at 4-6 years, and Schedule SDI is first dose of MMRV at 12 months and second dose at 18 months.

Table 6.4. Incremental cost utility ratios from healthcare and societal perspectives

	Healthcare perspective	Societal perspective[1]	Healthcare (no shingles) perspective	Societal (no shingles impact) perspective
Schedule LDI vs. No Vaccine[2]	Dominated	$1,285,353 per QALY gained	$8,447 per QALY gained	Dominant
Schedule SDI vs. No Vaccine[2]	Dominated	$1,170,209 per QALY gained	$8,955 per QALY gained	Dominant
Schedule SDI vs. Schedule LDI[2]	Dominated	$23,177 per QALY gained	$56,262 per QALY gained	Dominant

[1]All incremental cost-utility ratios are averaged over all model runs
[2]Control Group

The point ICURs based on the comparison of vaccination schedule showed schedule SDI was dominant (i.e. lower costs and higher QALY than schedule LDI) from the societal perspective and cost-effective from the healthcare perspective ($59,381-62,992 per QALY gained). However, the distributions of runs in **Figure 6.2a** demonstrated a wide range of possible ICURs when comparing the vaccination schedules, with values from across the spectrum on the cost-effectiveness plane. **Figure 6.2a** illustrates the uncertainty around that estimate; with some runs showing schedule SDI as cost saving (32%), some as cost-effective (50%) and other showing schedule LDI dominating (18%).

6.3.2. Sensitivity analysis

Most of the scenario analyses did not show a significant difference from our baseline scenarios, with chickenpox vaccination cost-ineffective from the societal perspective considering shingles, and cost-saving when not considering shingles (**Appendix H**, **Figure H-1** and **H-2**). However, no discounting of QALYs (i.e. one QALY lost in the present is worth the same as one QALY lost in the future) had a substantial impact on the benefits associated with chickenpox vaccination. Specifically, we found when we did not discount QALYs, the vaccination scenarios when considering shingles, had consistently higher QALYs per person-year than the no vaccination scenarios (**Figure 6.3**). Furthermore, lowering the duration of boosting to 2 years and using a waning immunity coefficient of 0.5 lead to a vast improvement in the cost-effectiveness of chickenpox vaccination when considering shingles (**Figure 6.3**). In all scenario analyses, while schedule SDI was on average more cost-effective than schedule LDI there was a wide range of outcomes, particularly when considering shingles. For instance, when we moved 15 % of vaccine hesitants to rejectors (low vaccine coverage) schedule SDI was more effective at preventing chickenpox infection on average but cost more than schedule LDI (**Appendix H, Figure H-1** and **Figure H-2**).

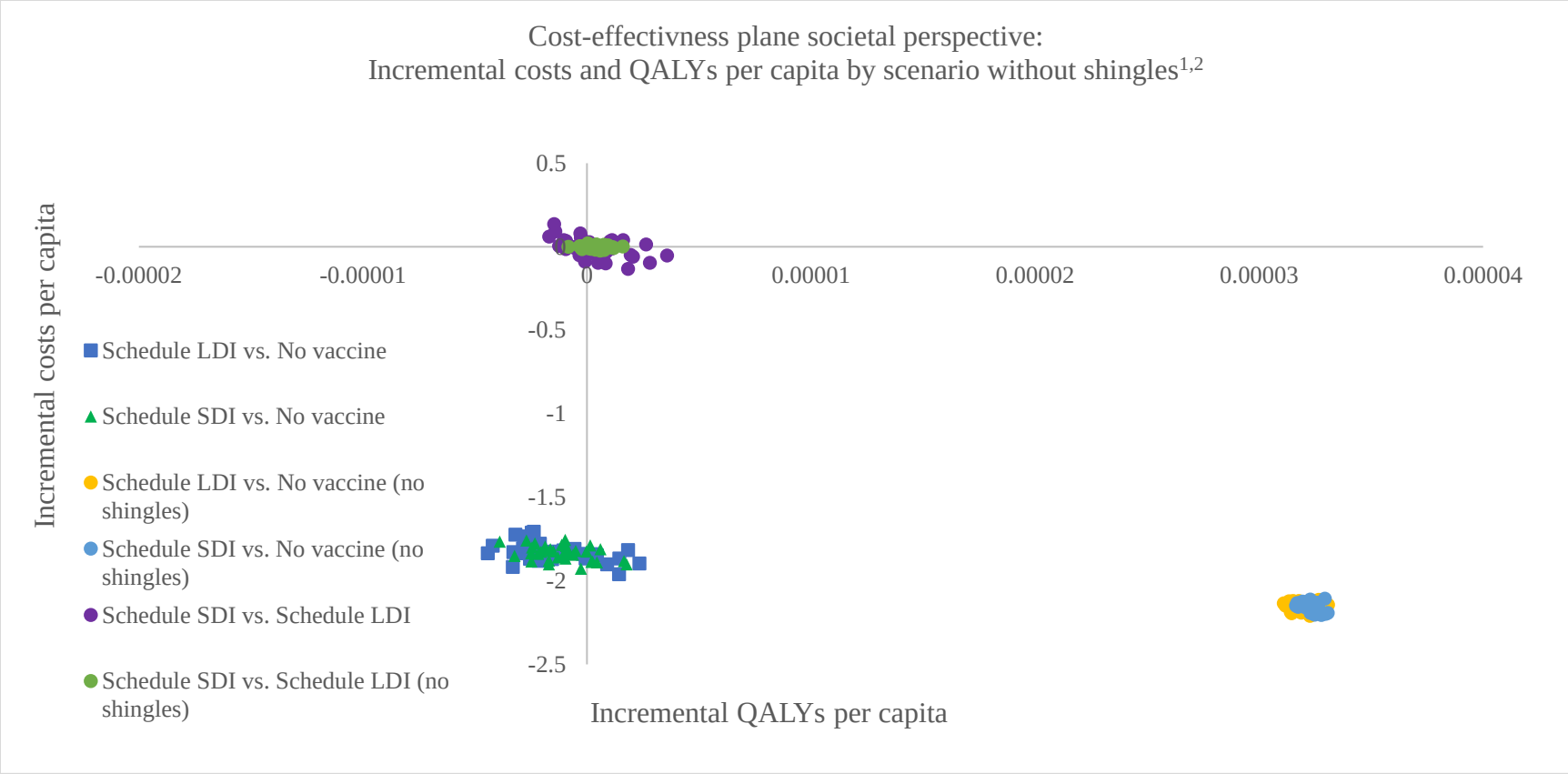


Figure 6.2a. Cost-effectiveness plane for chickenpox vaccination with and without shingles (societal perspective)

[1]Schedule LDI is 1st dose MMRV at 12 months and 2nd dose at 4-6 years, and Schedule SDI is first dose of MMRV at 12 months and second dose at 18 months.
[2]No shingles runs assumed there was no cost or loss of QALY associated shingles, therefore the differences between baseline, schedule LDI and schedule SDI were only based on differences in chickenpox incidence.

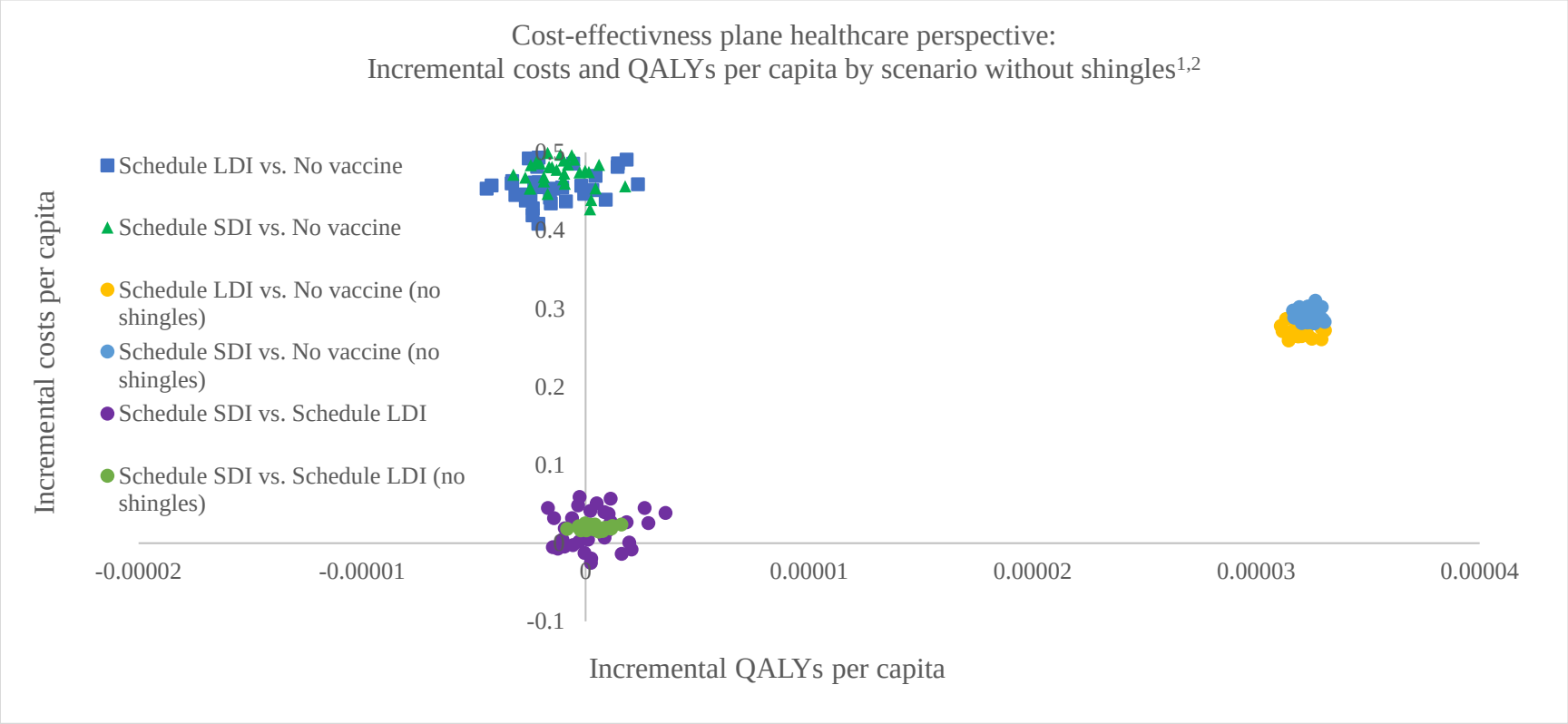


Figure 6.2b. Cost-effectiveness plane for chickenpox vaccination with and without shingles (healthcare perspective)

[1]Schedule LDI is 1st dose MMRV at 12 months and 2nd dose at 4-6 years, and Schedule SDI is first dose of MMRV at 12 months and second dose at 18 months.
[2]No shingles runs assumed there was no cost or loss of QALY associated shingles, therefore the differences between baseline, schedule LDI and schedule SDI were only based on differences in chickenpox incidence.

Figure 6.3. Scenario analysis cost-effectiveness plane: Median incremental costs and QALYs per capita with a shorter duration of exogenous boosting and no discounting of QALY, considering shingles (societal perspective)

[1]Duration of boosting = 2 years and waning of immunity rate = 0.45

[2]No discounting of quality adjusted life years; therefore, one QALY in the present is equal to one QALY in the future.

6.4. Discussion

This study is the first to use an ABM to conduct an economic evaluation of the chickenpox vaccine. Our ABM successfully estimated the cost-effectiveness of the chickenpox vaccination under a variety of scenarios (e.g. considering and ignoring the costs and benefits associated with shingles) in a 500,000-person population for 75 model-years. This is also the first study to compare the cost-effectiveness of different chickenpox vaccination schedules, a question particularly relevant to Canadian policy-makers [56].

Our results demonstrate that chickenpox vaccine is cost-saving from the societal perspective when ignoring the impact on shingles vaccine. These findings are consistent with previous research both globally [7,8,57] and in Canada [10,11], which highlight the large indirect cost benefits of chickenpox vaccination. At the same time, our model predicted that chickenpox vaccination would be highly cost-effective from the healthcare perspective (ICURs < 20,000), while most previous models, including Canadian studies, predicted that if we only consider the costs to healthcare the vaccine would not be cost-effective [10,11,57]. For example, Getsios et al. [10] estimated routine chickenpox vaccination would save Canada approximately $4 million from the societal perspective but would lead to an increase of $2.2 million from the healthcare perspective. While Brisson et al. [11] estimated that a universal infant vaccination program would cost $44,503 per life-year gained from the healthcare perspective and be cost-saving from the societal perspective.

The cost-savings from the societal perspective are largely due to the reduction in productivity losses, both from less time spent caregiving, as well as time off work due to illness. We estimated productivity losses accounted for a sizable percentage (75%) of the total costs for both shingles and chickenpox prior to vaccination. Hospitalization was the largest healthcare cost for shingles and chickenpox. However, recent research from Canada found shingles hospitalization rates were either declining and levelling over the past few years, while shingles medication costs were on the rise, up 37% from 1997/98 to 2011/12. These findings suggest drug costs may be a bigger factor in future cost-analyses. PHN also contributed to a substantial percentage of shingles healthcare costs in our model and in empirical studies [21]. Friesen et al. [21] estimate PHN was responsible for 41.6% of shingles hospital costs, 21.3% of medication costs and 49.7 % of drug costs, even though fewer than 10% of shingles cases got PHN.

When we incorporated shingles into our analysis, we found that vaccination was dominated by no vaccination (healthcare perspective) or was highly cost-ineffective (societal perspective). Again, these results were consistent with previous cost-effectiveness studies, which demonstrated that the increased severity of shingles infection, and the costs associated with treatment and productivity loss, generally outweighed the benefits of reducing chickenpox infection [11,57]. However, our model runs identified novel factors to consider when analysing chickenpox and shingles outcomes. First, while the point estimate for the ICUR of chickenpox vaccination considering shingles suggested vaccination was not cost-effective, even from the societal perspective, the range of values from the model runs tell a different story, as a substantial proportion of runs found that vaccination would be cost-saving. Second, the costs to society were consistently lower with vaccination than without. Therefore, while the point estimate ICURs suggested we should not vaccinate for chickenpox, policy-makers need to consider the overall picture of cost-effectiveness. For instance, there remains a large amount of uncertainty of the impact of chickenpox vaccine on shingles, which had a substantial effect on the cost-utility of the vaccine. Furthermore, most runs demonstrated that chickenpox vaccination would reduce overall costs, and many runs found chickenpox vaccination was cost-saving. All these factors may influence decision-making surrounding chickenpox vaccination.

Second, our results suggest that discounting QALY by 1.5% per year, as recommended by CADTH had a substantial impact on the cost-effectiveness of vaccination when considering shingles. Similar to what we observed in **Chapter 4**, under chickenpox vaccination scenarios our model predicted an initial increase in shingles, due to vaccination reducing the natural boosting of VZV immunity [16,58–60]. At the same time, we also predicted an ultimate decrease in shingles cases, which we postulated in **Chapter 4** was from the lowered risk of VZV latency following vaccination in comparison to natural infection, as observed in empirical studies [31,61,62]. With the increase of shingles occurring soon after the implementation of vaccination, and the overall decrease in shingles not occurring until many years into the model run, discounting QALY weighted the initial increase in shingles higher than the ultimate decrease in incidence. Discounting health effects have a particularly strong impact on public health interventions and prevention program, where effects, such as the reduction in shingles, are seen far in the future, but costs start to accrue immediately. Thereby leading to a bias against preventative measures [63]. It may be advisable to use a decreasing discount rate as

recommended by the World Health Organization [12] and NICE [64], to unsure we do not undervalue too heavily future benefits of vaccination. However, it is also important to consider if an increase in shingles does occur it may have a profound impact on the health care system in the near future, both raising costs and lowering the QALYs of the population.

Third, our sensitivity analysis further suggests, that if we assume a shorter duration of immunity following boosting and a faster waning of immunity rate, there is only a modest increase in shingles cases following vaccination, thereby drastically improving the cost-effectiveness of the chickenpox vaccination when considering the impact on shingles (**Figure 6.3A**). As we discussed in **Chapter 4**, there are many plausible values for boosting and waning of immunity, some of which lead to chickenpox vaccination being cost-saving and some of which result in high cost-effectiveness ratios. As the current empirical evidence suggests that the boosting of immunity may be short term and/or impact only a small percentage of the population, it is very possible the chickenpox vaccine may be cost-effective even when considering the impact of chickenpox vaccine on shingles [19,29,65]. As longer-term follow up data on shingles incidence following vaccination becomes available, it is essential we updated the assumptions in our model.

It is important to consider the differences in our model to previous chickenpox transmission models, and how these deviations may affect the cost-effectiveness of chickenpox vaccination. The two previous Canadian cost-effectiveness of universal chickenpox vaccination used deterministic realistic age-structured population models, which like our ABMs can capture the indirect effects of vaccination, including age of infection and herd immunity. However, there are further benefits to using an ABM; including the ability to capture exogeneous infection and represent a pattern of small but sustained outbreaks in the vaccinated population, similar to what is seen in empirical data [66]. Furthermore, agent-based modelling gave us the ability to represent the detailed vaccine, disease and health services histories of agents, and as such allowed us to capture a wide variety of costs and QALY gains and losses, including differences in costs/QoL for weakly infected, PHN, age-specific QoL for chickenpox infection, along with a variety of health utilization costs (physician, hospitalization, emergency room and medication). ABMs can further represent detailed elements of vaccination, including vaccine attitudes, uncertainties in vaccine coverage and – critically for this study – continuous waning of vaccine

immunity. Finally, ABMs allow for probabilistic analysis, with each model run leading to a different ICUR, based on the stochastics in disease transmission inherent in ABMs.

As our analysis took place several years following the implementation of the chickenpox within the Alberta childhood vaccine schedule, we could update prior parameter estimates. As such, this model provides a more accurate evaluation of the chickenpox vaccine's real-world cost-effectiveness. There were a few differences between our ex-post analysis (i.e. post-implementation) and the cost-effectiveness analyses conduct prior to vaccine implementation (ex-ante), both in terms of the inputs used, as well as the model outcomes. For instances, Brisson et al. [11] and Getsios et al. [10] both estimated the cost-effectiveness based one-dose vaccination, while most provinces and territories in Canada now have two dose schedules. Furthermore, the previous Canadian studies assumed only a certain percentage of individuals would be susceptible to vaccine waning of immunity and would wane at a relatively high rate [10,11]. These assumptions may account for the lower vaccine effectiveness and higher costs associated with infant vaccination described in Getsios et al. [10] and Brisson et al. [11].

Many of the assumptions made pre-vaccine implementation were similar to what we observed post-vaccine implementation, including assumptions about the costs of vaccination, coverage rates and primary vaccine failure. These assumptions resulted in some similar conclusions, including the cost-saving from the societal perspective and the impact of shingles on overall cost-effectiveness. Similar to our sensitivity analysis around coverage rates, Brisson et al. [11] found that varying the coverage of the chickenpox vaccine had little impact on the cost per life year gained for the infant vaccination strategy. These findings suggest that while cost-effectiveness studies done ex-post are important and can improve our understanding of the costs and effects of a particular vaccine, the results from ex-ante studies can still provide meaningful policy-relevant results.

Another element that may have altered the findings of our cost-effectiveness in comparison to the previous chickenpox vaccine cost-effectiveness studies, are changes to the CADTH guidelines outlining best-practices for economic evaluations in Canada [13,67]. For instance, neither Brisson et al. [11] (per life-year gained) or Getsios et al. [10] (per case avoided) conducted a cost-utility analysis, which CADTH recommends be the reference case analysis for all economic evaluations [13]. Type of economic evaluation is likely to make a significant difference in the cost-effectiveness of the vaccine, because while chickenpox and shingles may

not have a major impact on life years lost, they both can have major impacts on quality of life. Furthermore, as mentioned above we discounted QALY at a rate of 1.5% as recommend by CADTH, this had a significant impact on the cost-effectiveness of the chickenpox vaccine. In comparison, Brisson et al. [11] discounted both his costs and life years at a rate of 3% per year. Finally, Brisson et al. [11] only used a 30-year time horizon in their base case analysis. Currently CADTH recommends a time horizon long enough to capture all costs and benefits, which was the basis for running our model for 75-years post-vaccine implementation.

To our knowledge, this was the first cost-effectiveness analysis to measure the costs and benefits associated with different vaccine schedules. As the childhood vaccine schedule expands and becomes progressively more complex (e.g. multiple doses, combination vaccines), knowing the most effective and cost-saving method of administering a vaccine may be invaluable to policy-makers. Furthermore, estimates of the cost-effectiveness of different schedules can help inform decision-making on chickenpox vaccine implementation in countries that do not currently have a universal chickenpox vaccine program. While our point estimate ICUR suggests that schedule SDI was more cost-effective than schedule LDI from the societal perspective, some runs showed schedule SDI as more cost-effective and other suggested that LDI was the preferred strategy. The cost-effectiveness of schedule SDI is even less clear from the healthcare perspective, with an estimated ICUR at $$56,262 per QALY gained without shingles, and with LDI being the preferred strategy with shingles. However, healthcare costs for schedule SDI were artificially higher than schedule LDI due to the earlier start to 2nd dose vaccination, which meant there were a few years in the simulation where children were receiving 2nd dose vaccination in schedule SDI but not in schedule LDI. Furthermore, while schedule SDI was consistently more effective at decreasing chickenpox cases than schedule LDI, it also lead to a higher age of chickenpox infection and a slightly higher rate of shingles (**see Chapter 5**). These outcomes may have a negative impact on the cost-effectiveness of schedule SDI, as cases of chickenpox in adults and shingles are generally more severe (lower QoL) and costlier than the typical chickenpox case [14,17,20,21,28,57].

Our study had some notable limitations. First, our estimates for costs associated with chickenpox disease, specifically, chickenpox hospitalization [28], personal costs [20] and productivity loss [39], were significantly older than the estimates for shingles. While we did account for inflation in our analysis, the costs estimates may have changed significantly since

these studies were published. The economic burden of chickenpox may be an area for future analysis, to see how chickenpox costs have changed over time, particularly with the advent of vaccination and the increase in breakthrough cases. Second, while we needed to make fewer parameter assumptions than previous economic evaluations, there still remain multiple unknowns, including the impact of vaccination on shingles incidence and the long-term risk of vaccine waning of immunity. Therefore, it is imperative we continue to update the ABM and the chickenpox vaccine cost-effectiveness analysis as the evidence-base grows. Third, while the use of cost-utility analysis, specifically QALYs, are recommended by CADTH the estimation of utilities is often a complicated and imprecise process [13,68]. Different methods to measure the utilities used to calculate the QALY, including Standard Gamble and Health Utility Index Mark II, can often lead to various outcomes. For instance, in a study conducted by Brisson & Edmunds they found two different methods to calculate utilities for chickenpox led to different QoL estimates [45]. Furthermore, the population surveyed for the utility analysis (e.g. patients, general population, country) can also affect the overall results [68]. Therefore, the utilities we used in this analysis are hard to validate [69]. Third, given the unknowns surrounding the costs and utilities associated with chickenpox and shingles used in this analysis, it may have been prudent to complete a probabilistic sensitivity analysis on these values. A probabilistic sensitivity analysis would have allowed us to determine the percentage of runs that were cost-effective or cost-saving based on a range of cost and utility estimates. However, as the model itself was already probabilistic and the stochastics in our model already provided a range of possible costs and outcomes for each run we did not want to input more uncertainty in the model by using distributions for the costs and effects. Furthermore, we did not test the impact of a 3% discount rate, which is a value commonly used in international literature. Finally, a cost-effectiveness analysis should be only one factor in decision-making, as it can only capture some of the benefits of a vaccination program. Therefore, it is imperative other evaluations are conducted on chickenpox vaccination, including equity evaluations (i.e. does the chickenpox vaccine benefit all population groups equally) and availability evaluations (is the vaccine reaching those who most need it?).

Our ABM could be used for future cost-effectiveness; including testing a wider variety of chickenpox schedules, particularly those being used throughout Canada, for example in Ontario (V-15 months, MMRV 4-6 years) and Quebec (MMRV- 18 months, V- 4-6 years). We could

further use our ABM to simulate the cost-effectiveness of the new shingles vaccine, as policy-maker will need to decide whether to include it in the publicly-funded vaccination program. In future analyses we aim to complete wider range of scenario analyses, including the impact of a higher rate of shingles following chickenpox vaccination, updated health and productivity costs for chickenpox disease, increased variation in vaccination costs, and potentially a threshold analysis to determine at what rate of primary and secondary vaccine failure there is an obvious preference for schedule LDI or schedule SDI.

6.5. Conclusions

Our findings suggest that chickenpox vaccination is cost-saving or cost-effective from the societal and healthcare perspective when not considering the impact on shingles. In fact, chickenpox vaccination may even be cost-effective when accounting for the additional costs associated with shingles. This is an important finding for countries which have delayed vaccination for fear of the impact on shingles incidence [15]. However, to fully understand the impact of the chickenpox vaccine on shingles and therefore its cost-effectiveness we need to continue to monitor VZV epidemiological and biological studies. Moreover, in this analysis we determined a chickenpox vaccination schedule with a reduced amount of time between 1st and 2nd dose (schedule SDI) may lead to slightly lower costs and higher QALY than a longer time between doses (schedule LDI), and therefore may be the better choice for countries just setting up a chickenpox vaccination program. However, as the results were not conclusive, other contributing factors, such as the type of vaccine implemented (e.g. V versus MMRV), if the vaccine can be administered at the same time as other vaccines, public perception, vaccine coverage at different ages, should be considered and may play a larger role in the ultimate timing of chickenpox vaccination doses.

6.6. References

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CHAPTER 7- CONCLUSIONS

7.1. Overall findings and their relevance to research and policy

This thesis aimed to address four research questions, (1) the scope of research available on economic evaluations of vaccines in Canada, (2) the impact of chickenpox vaccination on shingles disease outcomes under various theories of waning and boosting of varicella zoster virus (VZV) immunity, (3) the impact of two different chickenpox vaccination schedules on chickenpox and shingles disease outcomes in Alberta, and (4) the overall cost-effectiveness of chickenpox vaccine, as well as the cost-effectiveness of two different chickenpox vaccine schedules.

Tackling these research questions can help improve shingles and chickenpox diseases control strategies, both in Alberta and internationally. This research can provide guidance to policy-makers interested in using agent-based modelling to inform decision-making; as well as improve the approach to, and reporting of, economic evaluations of vaccines in Canada. This chapter will highlight some of the key limitations of the research, including limitations with the two main methodological approaches used throughout this thesis, agent-based modelling and economic evaluation. Furthermore, this chapter will note key areas for future research, such as increasing the number of post-implementation economic evaluations and potential future applications for our chickenpox and shingles agent-based model (ABM).

7.1.1. Shingles control

Chapter 4 of this thesis presents novel findings relevant to chickenpox vaccination and shingles control. While previous models generally predicted a substantial increase in shingles incidence following chickenpox vaccination, this thesis inextricably linked the rise in shingles with the boosting and waning of VZV immunity assumptions in the model [1–3]. **Chapter 4** highlighted boosting and waning of VZV immunity scenarios that fit empirical data; while some of these scenarios predicted large increases in shingles cases following chickenpox vaccination, many of them predict only a small, potentially negligible rise in shingles incidence. Furthermore, current research suggests that individuals vaccinated with chickenpox have a significantly lower risk of VZV remaining latent in the body, and therefore a lower risk of the virus reactivating in the form of shingles. As such, our model predicted that chickenpox vaccination could ultimately

reduce shingles incidence to a very low rate. These results were validated in recent epidemiological studies [4,5].

These findings may help inform decision-making surrounding the chickenpox vaccine. Many countries have resisted implementing the chickenpox vaccine due to concerns about its impact on shingles. Our model shows that the impact on shingles could be significantly smaller than originally estimated. Moreover, the benefits of reducing the population susceptible to shingles may ultimately outweigh the initial increase in cases. The results of this thesis highlight the need for better estimates of duration of VZV immunity following exogenous boosting (i.e. time gained in protection against shingles reactivation following a boosting event) and risk of reactivation in chickenpox vaccinees, so researchers can estimate the true impact of chickenpox vaccination on shingles.

7.1.2. Chickenpox control

While **Chapter 4** focused on the impact of chickenpox vaccination on shingles, **Chapters 5** and **6** highlighted its effect on chickenpox control**. Chapter 5** demonstrated that chickenpox vaccination is very effective at reducing the overall chickenpox incidence and predicted, based on current estimates of primary and secondary vaccine failure that it would continue to remain effective into the future. However, chickenpox was not eradicated in our population, likely due to the sustained transmission of VZV from shingles and due to cases being imported from outside the model (exogenous infection). These findings illustrate a more optimistic future to chickenpox than previous models that tested the impact of chickenpox vaccination over time, and commonly predicted a steady increase in chickenpox cases years following vaccine implementation [3].

In general, we found that chickenpox vaccination was likely cost-effective in Alberta over a 75-year time-period. While we did observe that an increase in shingles incidence following vaccination could drastically reduce the cost-effectiveness of the chickenpox vaccine, this was highly dependent on the duration of immunity following boosting and waning of immunity rate for VZV. As we demonstrated in **Chapter 4**, there are many plausible values for duration of immunity following boosting and waning of immunity that led to only a small increase in shingles cases and had a minimal impact on the cost-effectiveness of the vaccine. Furthermore, the majority of model runs found that chickenpox vaccination would be cost-effective from the societal perspective, even when considering the impact on shingles. Our results were also highly

sensitive to the discounting rate for the benefits of vaccination as a lot of the gains, including the ultimate decrease in shingles cases, were observed many years following the implementation of the vaccine. These findings demonstrate that chickenpox vaccine may be cost-effective even when accounting for the impact on shingles.

Perhaps more relevant to Canadian policy were our findings on the optimal chickenpox vaccine schedule. Our study in **Chapter 5** found that schedule SDI, which administered the second dose chickenpox vaccination shortly after first dose (18 months instead of at 4-6years in schedule long dosing interval- LDI), resulted in significantly fewer breakthrough cases. The impact of schedule on overall chickenpox cases was less clear; however, 100% of paired model runs showed a lower chickenpox incidence with schedule SDI than schedule LDI. These findings may be important for policy makers considering the most effective way to implement the chickenpox vaccine. However, while we found that schedule SDI had lower costs and higher quality-adjusted life-years from the societal perspective (with no shingles), this was not a consistent finding across all model runs, with some runs showing schedule LDI as dominant. Therefore, while schedule SDI may be the better choice for countries setting up new chickenpox vaccination programs, policy makers may want to consider other factors when scheduling the chickenpox vaccine, including public perception, ease of schedule implementation/change and the impact of the schedule on other antigens included in the combination vaccine (e.g. measles, mumps, rubella – MMR).

7.1.3. ABMs to inform policy-making

To conduct all the experiments described in this thesis, we constructed one of the first ABMs for chickenpox and shingles infection and vaccination. We have made this model open source (**Chapter 4 – Data Reference 1**) so future researchers can use it to answer their own research questions. Agent-based modelling is a relatively new technique used in economic evaluations. However, this modelling technique can overcome previous economic evaluation modelling limitations, including linearity (i.e. the inability to account for externalities, unintended consequences), homogeneity (i.e. lack of consideration of individual-level differences that impact population-level disease outcomes) and stationarity (i.e. the fact that how people interact and move through a population determines the spread of disease) [6]. With only a few examples of economic evaluations using ABMs in the literature [7–10], the description

presented in this thesis as to how to use an ABM to calculate cost-effectiveness may prove useful to researchers considering similar modelling techniques for their own economic studies.

7.1.4. Economic evaluations of vaccines in Canada

By outlining the gaps, the important trends, and the key strengths and weaknesses in the economic evaluation of vaccines literature in Canada, **Chapter 2** can serve as a guiding document on economic evaluation of vaccines in Canada for policy makers. Prior to this thesis, Canada, like most countries, had not reviewed and synthesized the literature on economic evaluations of vaccines, meaning they had very little knowledge of the coverage or quality of this research. As other countries start to produce similar evidence, comparing reporting strategies, methods and results between countries could prompt an international discussion on the major gaps in the literature and the quality of economic evaluations, and in doing so lead to improvements in the standardization and transparency of these studies. Furthermore, Canadian researchers can use this review to build upon past economic evaluations by addressing some of the gaps and weaknesses in the literature. As illustrated in **Chapter 2**, the number of vaccine-related economic evaluations has substantially increased in the last few years. Cost-effectiveness analyses are being used increasingly to make decisions and recommendations around the implementation of, and funding for, vaccines in Canada. Therefore, it is important to ensure economic evaluations produced in Canada are transparent and of high quality. By outlining the current state of the research, including limitations, we can promote improvement in the usefulness, quality and applicability of vaccine-related economic evaluations and the decisions they inform.

7.2. Thesis limitations

7.2.1. Limitations of agent-based modelling

Building an ABM is a complicated process, as it is time-consuming to create and run the model, and it is data-consuming (i.e. wide variety of detailed data is required to input into the model). Individual-level data is often difficult to extract from the literature; for instance, in our model we estimated the individual probability of primary and secondary chickenpox vaccine failure and then compared our model findings to the more readily available empirical data on population-based vaccine effectiveness. To obtain appropriate values for a range of parameter estimates in our model, we conducted a review of a wide variety of literature, including data on

Canadian and Albertan demographics (i.e. age-distribution, mortality, birth rates), VZV immunology, chickenpox and shingles epidemiology and healthcare utilization, as well as chickenpox vaccine effectiveness and coverage. As described in **Chapters 4** and **5,** our model required substantial testing and validation to ensure it was providing results similar to what was observed in the empirical data. Furthermore, debugging problems in the agent-based environment is often difficult and time-consuming [11].

Moreover, the intricacies of an ABM model may make presenting results to policy-makers difficult. However, ABMs in Anylogic® include some useful graphical features, for example a network diagram showing disease transmission (**Appendix I**), which allows users to observe a disease spreading from agent-to-agent during an outbreak and identify which agents are protected through vaccination. It is important users of ABMs use these graphical capabilities to present the methods and results of their model in an informative and accessible way.

7.2.2. Limitations of economic evaluations

It is important to note some of the limitations of economic evaluations as a decision-making tool, particularly as they only tell one side of the story. In many instances, it is imperative that policy makers undertake other forms evaluations, including those studying the efficacy (can it work?); effectiveness (does it work?); equality/equity (does it work on everyone? How does it affect the most vulnerable?); and the availability (is it reaching those in need?) of the intervention [12]. Economic evaluations often do not account for the fact that costs and consequences of diseases and interventions vary among population groups (e.g. stratifying the cost-effectiveness by risk group), making consideration of the equity of the intervention particularly important. Russell et al. [13] found in Alberta prior to adding chickenpox to the universal vaccination schedule, there were disparities in chickenpox disease; specifically, those with lower socio-economic status (based on a SES-proxy measure) and First Nations individuals had higher chickenpox incidence rates. Following vaccination, there was a dramatic decrease in the disparities between high and low SES-proxy, suggesting publicly-funded vaccination may help reduce disparities [13]. However, they discovered chickenpox rates in First Nations individuals remained higher than other groups following vaccination, suggesting a lack of equity in the delivery and/or the uptake of the vaccine [13]. There was no evidence of differences in shingles incidence by SES-proxy [13].

Furthermore, productivity loss is valued differently across groups. For instance, there is the tendency to undervalue the impact of the disease on older or unemployed individuals. In our analysis older individuals were less likely to be part of the labour force and therefore disease in these individuals, while typically more severe, was associated with smaller productivity losses. Furthermore, over-emphasizing the importance of the cost-effectiveness of an intervention may result in a focus on diseases that are economically expensive but do not have a large impact on morbidity or mortality [14]. One could argue this is the case with chickenpox, as the aim of chickenpox vaccination is to reduce the incidence of a generally minor infection in a large number of people.

7.3. Future work

7.3.1. Economic evaluations post-vaccine implementation

In **Chapter 2** of this thesis we identified a lack of economic evaluations conducting post-vaccine implementation as a limitation in the Canadian vaccine cost-effectiveness literature. The results of **Chapter 5** and **6** on the effectiveness and cost-effectiveness of different chickenpox schedules demonstrates post-implementation studies can provide valuable information for researchers and policy makers looking to run an effective vaccination program. Policy-makers and researchers can use post-implementation economic evaluations to ensure the current vaccination programs are run efficiently and effectively. For instance, more research is needed on the cost-effectiveness of providing a booster dose at different ages for pertussis in Canada, or the cost-effectiveness of a catch-up dose off the MMR vaccine in individuals who only received one dose. However, it may be difficult to find the political will to support these types of studies, as there is often resistance, both politically and publicly, to discontinuing a health intervention that is already provided by the government.

7.3.2. Future applications of the chickenpox ABM

The ABM outlined in this thesis could be used to answer a variety of research questions, including how changing contact patterns between agents alters the number and type of VZV boosting events, and what other factors influence an individual's chance of developing shingles. Furthermore, our model could help identify other reasons for the observed increase of shingles incidence in the past few years [15,16]. There are many theories for why we may see this increase, including changes in shingles reporting, increases in the number of

immunocompromised individuals, and fewer contacts with chickenpox cases; our model could provide a platform to test these theories. Moreover, our ABM can study the effectiveness and cost-effectiveness of a wider variety of chickenpox vaccine schedules, taking into account the impact of different types of vaccines (MMRV vs. V) and adverse events (e.g. febrile seizures [17]), as well as vaccine uptake at different age groups.

Moreover, even though we did not use shingles vaccination in any of the thesis experiments, the ABM includes a shingles vaccination statechart and shingles protected state, and it therefore has the capability to measure the effectiveness and cost-effectiveness of implementing a universal shingles vaccination program in Alberta. An important next step would be to update the research on the cost-effectiveness of herpes zoster vaccine in Canada [18], including the cost-effectiveness of the new shingles vaccines [19,20].

A future goal is to make our model available for policy makers to ask their own 'what-if' questions and to test the impact of their decisions prior to implementation. Modifying our ABM so that it is more user-friendly with an easy to use interface would make it more accessible to policy-makers and program administrators alike. A similar project is currently underway for a pertussis ABM with Alberta Health Services, so policy-makers can enter their own parameter values into the ABM and test different pertussis outbreak immunization response strategies to see their effectiveness at reducing the length and size of the pertussis outbreak [21].

Although not appropriate for all economic evaluations, ABM is a valuable tool for conducting cost-effectiveness studies, particularly where there is the potential for multiple externalities and indirect consequences of vaccination [6]. It may also be valuable where the contact network plays a crucial role in how a disease spreads, for instance in sexual transmitted diseases and tuberculosis. The choice of model type and structure is an important one, as studies show that it can play a significant role in the cost-effectiveness of the vaccine and can drastically change the results of the analysis [22]. However, researchers should balance the usefulness of agent-based modelling with the time and data requirements needed to build these complex models. Researchers should generally follow the recommendation of the Canadian Agency for Drugs and Technologies in Health that the modelling approach should be "no more complex than is necessary to address the decision problem" [22, p.19]. It is particularly important that researchers work together to build and update these models, so that one model can be used to inform many research questions. It is our hope that researchers and research groups will continue

to use our chickenpox and shingles ABM to answer questions relevant to policy makers and scientists alike.

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APPENDIX A

ETHICS

Notification of Approval (Renewal)

Date: August 8, 2016

Amendment ID: Pro00052642_REN2

Principal Investigator: Alexander Doroshenko

Study ID: MS3_Pro00052642

Study Title: Public health response to outbreaks of vaccine-preventable diseases: evaluation of immunization campaigns as an outbreak response measure

Sponsor/Funding Agency: Alberta Health & Wellness
University of Alberta Faculty of Medicine and Dentistry

AH
POMD

PSCO-Managed Funding	Project ID	Project Title	Speed Code	Other Information
	View RES0025115	AB Health - communicable diseases project	ZC411	
	View RES0027704	AB Health - communicable diseases project	ZA884	

Approval Expiry Date: Monday, August 7, 2017

Thank you for submitting this renewal application. Your application has been reviewed and approved.

This re-approval is valid for another year. If your study continues past the expiration date as noted above, you will be required to complete another renewal request. Beginning at 30 days prior to the expiration date, you will receive notices that the study is about to expire. If you do not renew on or before the renewal expiry date, you will have to re-submit an ethics application.

All study related documents should be retained so as to be available to the Health REB upon request. They should be kept for the duration of the project and for at least 5 years following study completion.

Sincerely,

Anthony S. Joyce, Ph.D.
Chair, Health Research Ethics Board - Health Panel

APPENDIX B

ADDITIONAL FILES CHAPTER 2

Table B.1. Keyword search strategy to identify peer-reviewed articles

Immunization keywords	Economic evaluation keywords	Canadian keywords
Immunization	Economic evaluation	Canada
Immunizations	Economic evaluations	British Columbia*
Immunisation	Cost benefit	Alberta*
Immunisations	Cost effective	Saskatchewan*
Immunized	Cost effectiveness	Manitoba*
Immuni* program	Cost utility	Ontario*
Immuni* programs	Cost*	Quebec*
Immuni* schedule	Cost benefit analysis	Maritimes
Immunization, Secondary	Cost benefit analyses	New Brunswick
Mass Immuni*	Cost effectiveness analysis	Nova Scotia
Vaccine	Incremental cost effectiveness	Prince Edward Island
Vaccines	Incremental cost utility	PEI
Vaccination	Incremental economic evaluation	Northwest Territories
Vaccinations	Models, economic	Nunavut
Vaccinating	Cost saving*	Yukon
Mass vaccination	Cost of illness	Toront*
Vaccin* program	Cost and cost analysis	Calgar*
Vaccin* programs	Cost minimization	Edmonton*
		Vancouver*
		Winnipeg*
		Ottawa*
		Halifax*
		Saskatoon*
		Regina
		Victoria

APPENDIX C

FULL LIST OF PARAMETER VALUES FOR CHAPTER 4

Parameter	**Values**
Total Population	500,000
Population Density- Urban	0.03
Population Density- Rural	0.02
1st dose chickenpox vaccination	On
2nd dose chickenpox vaccination	On
ProbabilityOf1stDoseVaccination	0.97,0.75,0.03
ProbabilityOf2ndDoseVaccination	0.979,0.821,0.333
ProbabitlityOf1stDoseEffective	1-uniform (0.16,0.24)
ProbabilityOf2ndDoseEffective	1-uniform (0.05,0.16)
ProbabilityCatchupGivenVacc	0.55
Weight_vacc_acceptor	65
Weight_vacc_hesitator	30
Weight_vacc_rejector	5
Shingles Vaccination	Off
Exogenous Infection Rate	17.83
Pref. Mixing Age	1-9
Duration of exogenous boosting	See different calibration experiments below
Shingles connection range modifier	0.124
Shingles waning coefficient	See different calibration experiments below
Probability of shingles reactivation	0.05
Initialization	EQ_NoVacc
Enable bimodal shingles immunizing timer	Checked
Min_ageForDosAccel	0
Max_ageForDosAccel	19
ProbabilityOrDosAcc	0.05
DurationCP	Uniform (5,9)
durationCPweak	Uniform (4,8)
probCPDisease on Contact	0.781
probCPDiseaseOnContactWithShingle	0.2343
probCPDiseaseOnContactWithBreakthrough	0.2343
probBreaktrhoughCPDiseaseOnExposure	0.03
timeToRecoveryCP	Uniform (0,4) *day
timeToNotInfectiousShingles	Uniform (7,20) * day
WaningOfImmunityRateShingles	0.04*waningOfImmunityCoefficientShingles
shinglesRecurrenceRate	Uniform (0.0022,0.0076)
connectionRange_Pref	21.245
connectionRange_Norm	8.958
baseContactRate_Pref	20
baseContactRate_Norm	3
burnPeriod	75 years

Total Model Run	175 years

Main experiment 1:

Parameter	Values
Duration of Exogenous Boosting	5 years
Shingles waning coefficient	0.63

Main experiment 2:

Parameter	Values
Duration of Exogenous Boosting	4 years
Shingles waning coefficient	0.6

Main experiment 3:

Parameter	Values
Duration of Exogenous Boosting	6 years
Shingles waning coefficient	0.68

Main experiment 4:

Parameter	Values
Duration of Exogenous Boosting	2 years
Shingles waning coefficient	0.5

Main experiment 5:

Parameter	Values
Duration of Exogenous Boosting	3 years
Shingles waning coefficient	0.55

Main experiment 6:

Parameter	Values
Duration of Exogenous Boosting	7 years
Shingles waning coefficient	0.74

APPENDIX D

ADDITIONAL FILES CHAPTER 4

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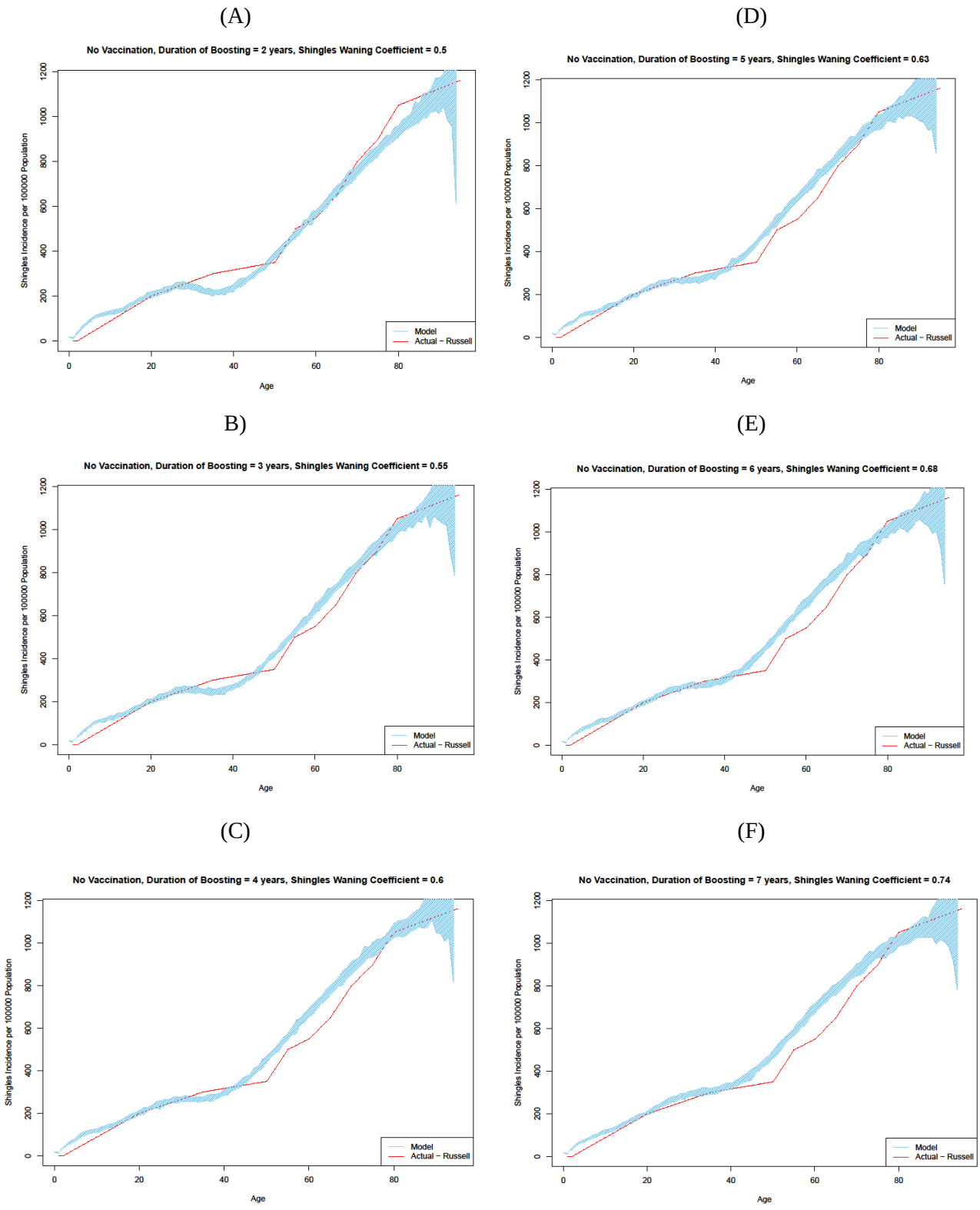
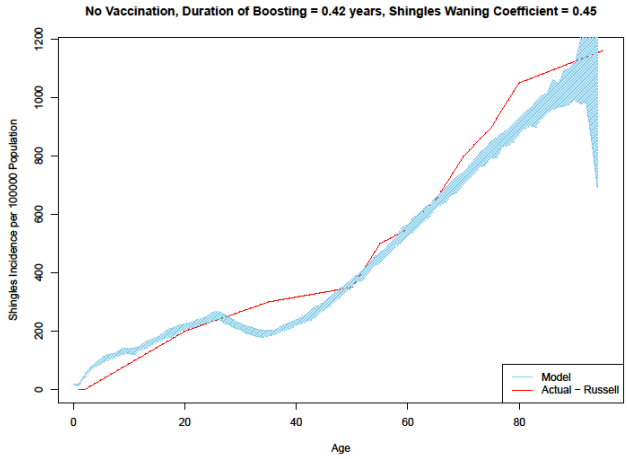
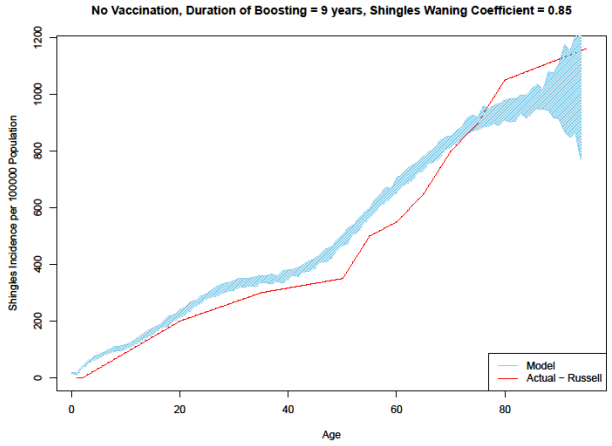


Figure D.1. Simulated and empirical age-specific incidence rate for scenarios that met calibration with various duration of boostings and waning of immunity rates (A) DoB= 2 years, WoI= 0.5 (B) DoB= 3 years, WoI= 0.55 (C) DoB= 4 years, WoI= 0.6 (D) DoB= 5 years, WoI= 0.63 (E) DoB= 6 years, WoI= 0.68 (F) DoB= 7 years, WoI= 0.74. (Blue polygons represent the min and max of the 30 simulated runs)

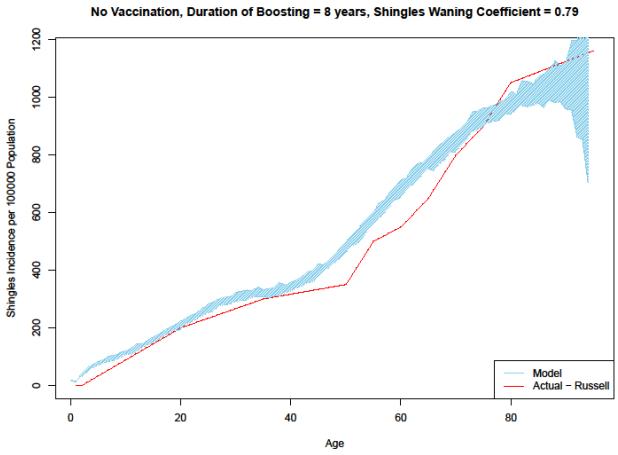
(A)



(C)



(B)



(D)

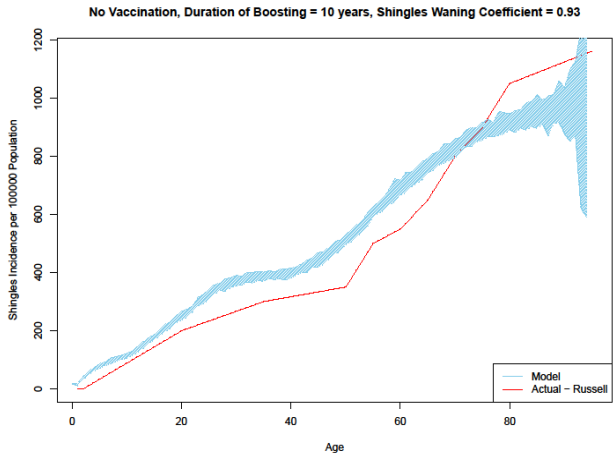
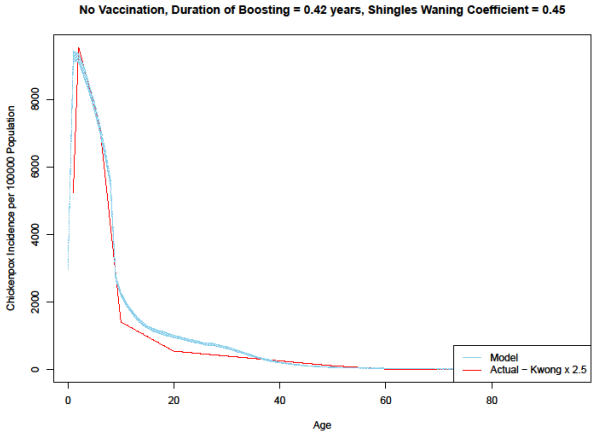
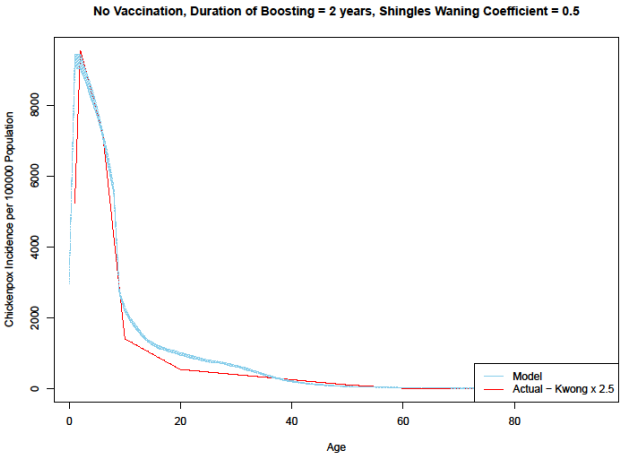


Figure D.2. Simulated and empirical age-specific incidence rate for scenarios that did not met calibration with various duration of boostings and waning of immunity rates (A) DoB= 0.42 years, WoI= 0.45 (B) DoB= 8 years, WoI= 0.79 (C) DoB= 9 years, WoI= 0.85 (D) DoB= 10 years, WoI= 0.93. (Blue polygons represent the min and max of the 30 simulated runs)

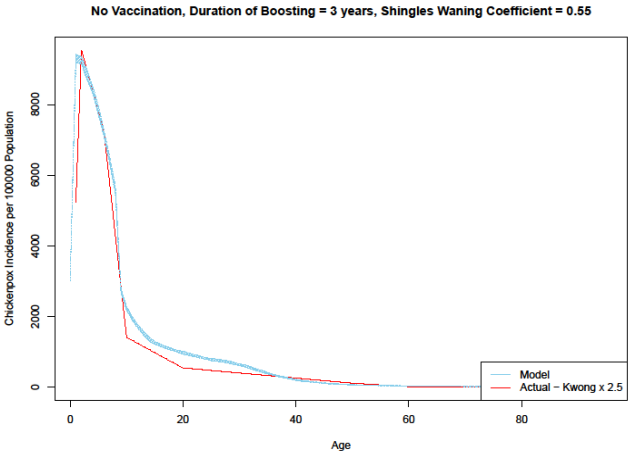
(A)


No Vaccination, Duration of Boosting = 0.42 years, Shingles Waning Coefficient = 0.45
Chickenpox Incidence per 100000 Population
0
2000
4000
6000
8000
0
20
40
60
80
Age
Model
Actual − Kwong x 2.5

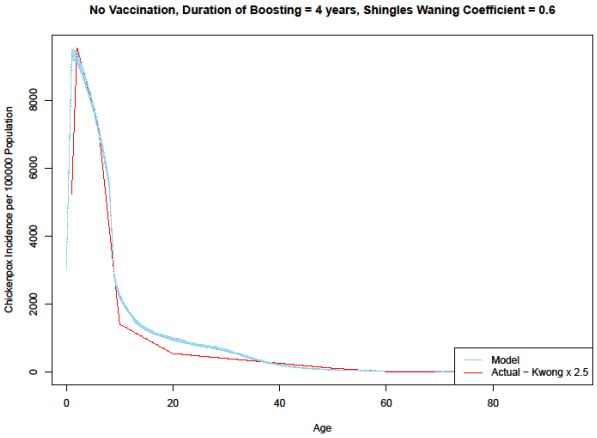
(B)


No Vaccination, Duration of Boosting = 2 years, Shingles Waning Coefficient = 0.5
Chickenpox Incidence per 100000 Population
0
2000
4000
6000
8000
0
20
40
60
80
Age
Model
Actual − Kwong x 2.5

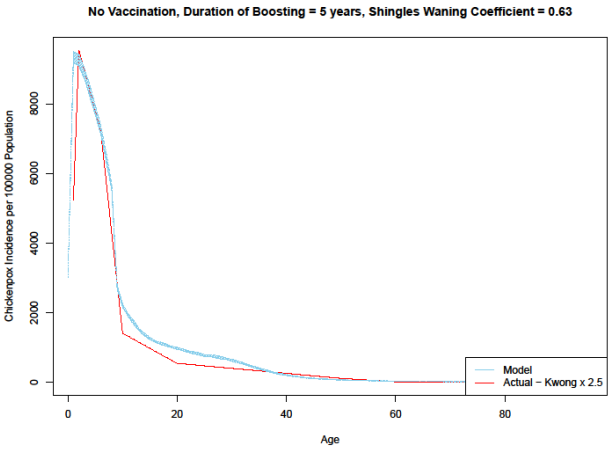
(C)


No Vaccination, Duration of Boosting = 3 years, Shingles Waning Coefficient = 0.55
Chickenpox Incidence per 100000 Population
0
2000
4000
6000
8000
0
20
40
60
80
Age
Model
Actual − Kwong x 2.5

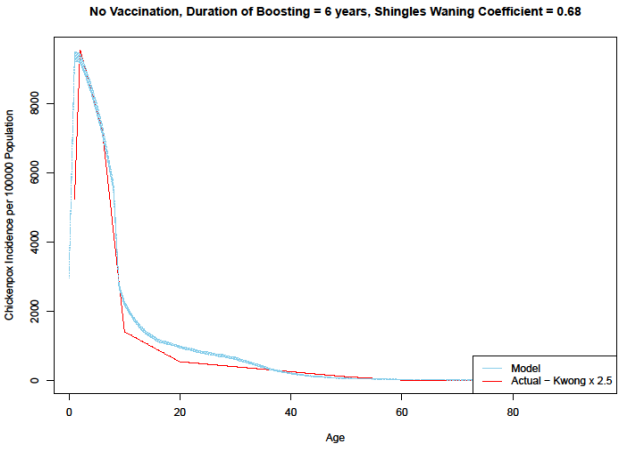
(D)


No Vaccination, Duration of Boosting = 4 years, Shingles Waning Coefficient = 0.6
Chickenpox Incidence per 100000 Population
0
2000
4000
6000
8000
0
20
40
60
80
Age
Model
Actual − Kwong x 2.5

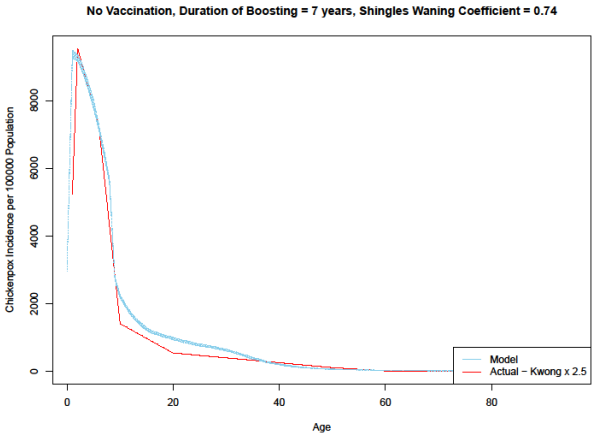
(E)


No Vaccination, Duration of Boosting = 5 years, Shingles Waning Coefficient = 0.63
Chickenpox Incidence per 100000 Population
0
2000
4000
6000
8000
0
20
40
60
80
Age
Model
Actual − Kwong x 2.5

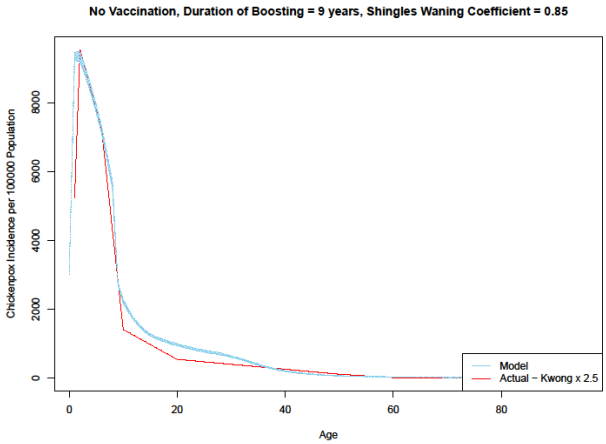
(F)


No Vaccination, Duration of Boosting = 6 years, Shingles Waning Coefficient = 0.68
Chickenpox Incidence per 100000 Population
0
2000
4000
6000
8000
0
20
40
60
80
Age
Model
Actual − Kwong x 2.5

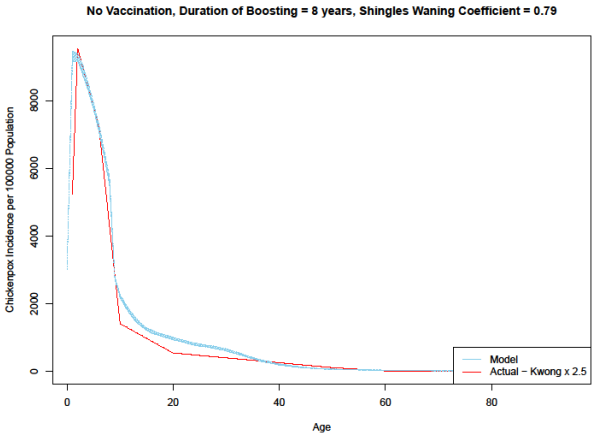
(G)



(I)



(H)



(J)

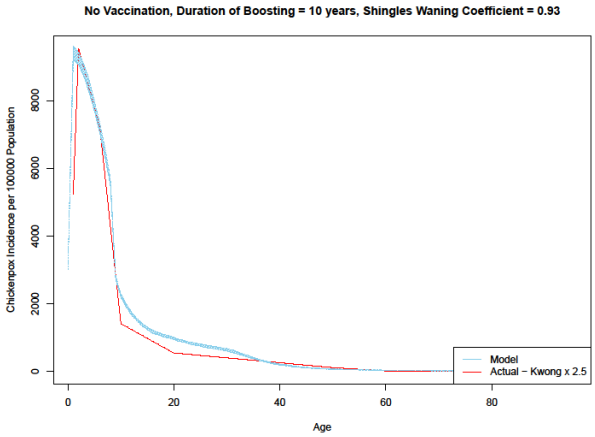


Figure D.3. Simulated and empirical age-specific chickenpox incidence for different duration of boosting and waning of immunity, all scenarios that met calibration (A) DoB= 0.42 years, WoI= 0.45 (B) DoB= 2 years, WoI= 0.5 (C) DoB= 3 years, WoI= 0.55 (D) DoB= 4 years, WoI= 0.6 (E) DoB= 5 years, WoI= 0.63 (F) DoB= 6 years, WoI= 0.68 (G) DoB= 7 years, WoI= 0.74 (H) DoB= 8 years, WoI= 0.79 (I) DoB= 9 years, WoI= 0.85 (J) DoB= 10 years, WoI= 0.93. (Blue polygons represent the min and max of the 30 simulated runs)

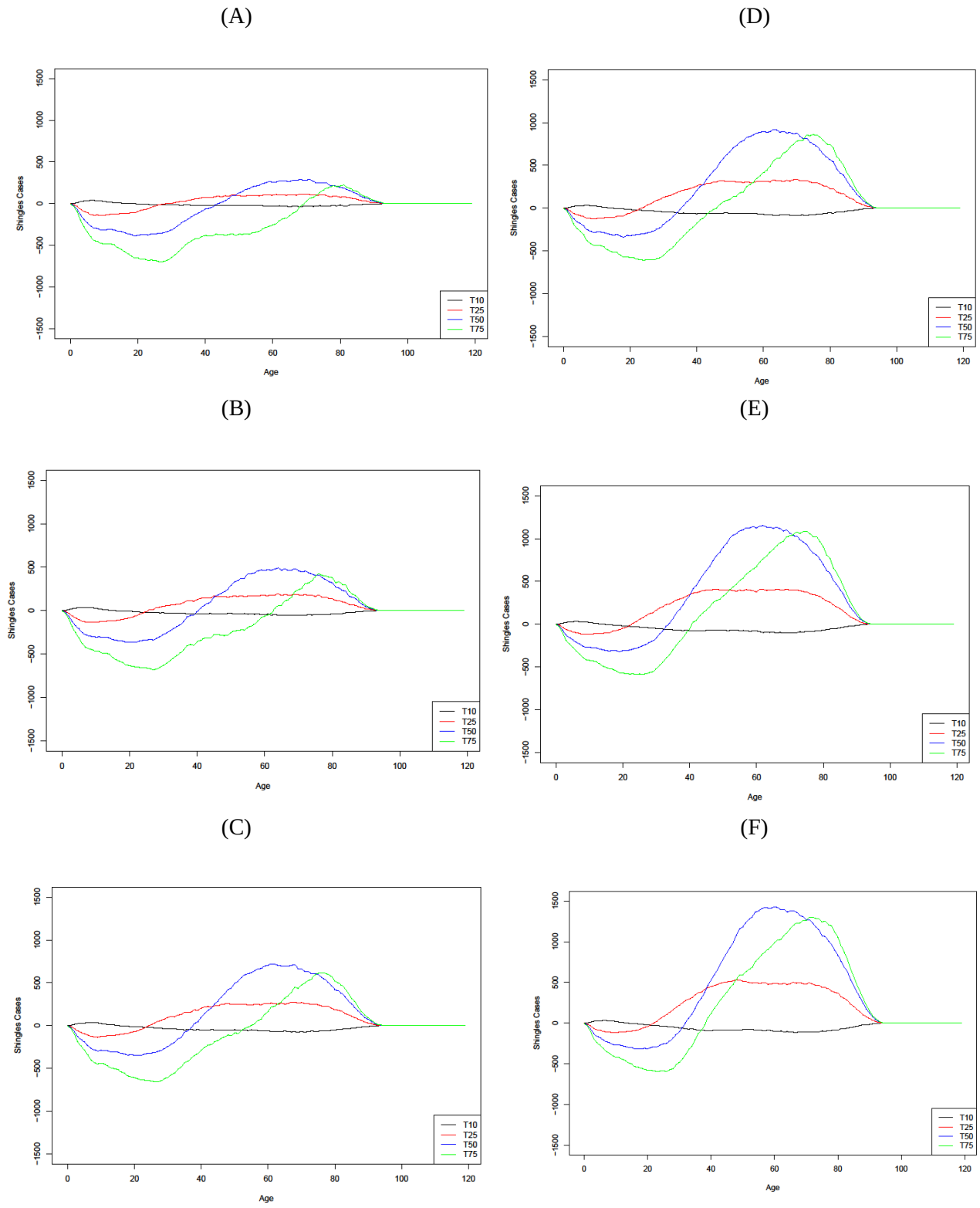


Figure D.4. Number of shingles cases by age at time 10, 25, 50 and 75 years by scenario (A) DoB= 2 years, WoI= 0.5 (B) DoB= 3 years, WoI= 0.55 (C) DoB= 4 years, WoI= 0.6 (D) DoB= 5 years, WoI= 0.63 (E) DoB= 6 years, WoI= 0.68 (F) DoB= 7 years, WoI= 0.74

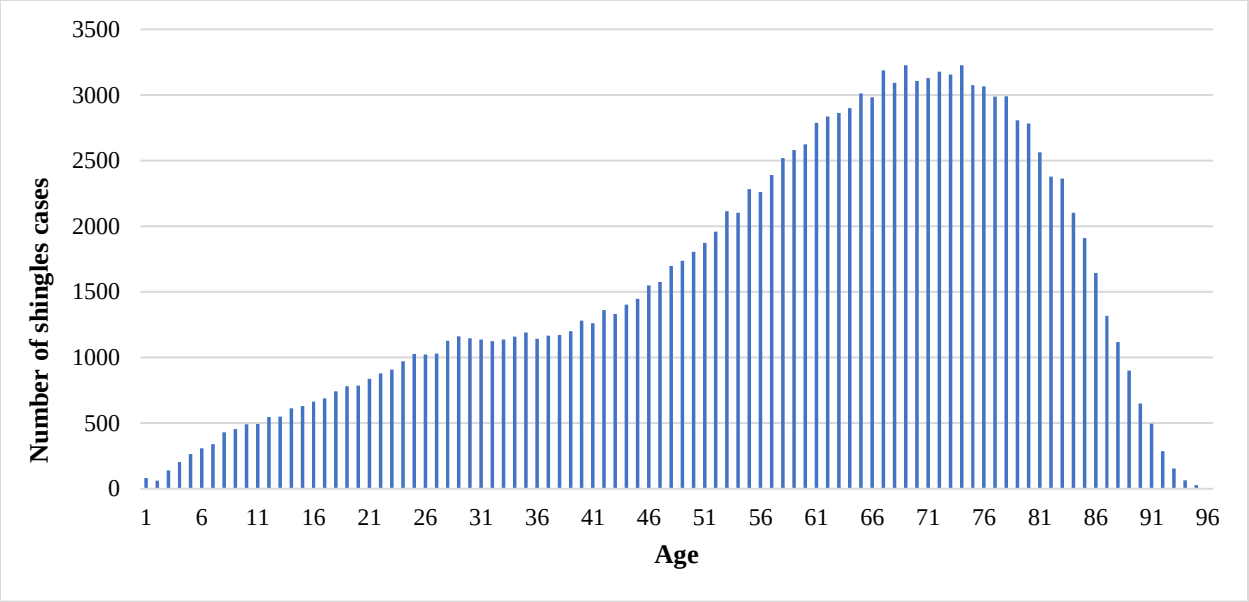
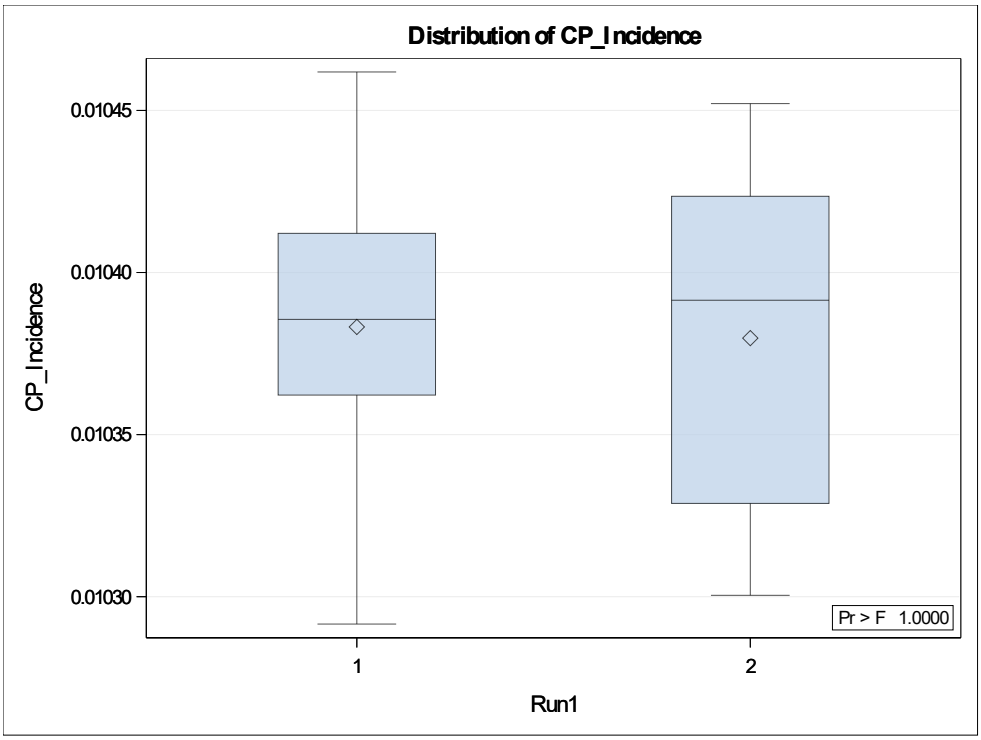


Figure D.5. Age distribution of shingles cases in baseline

APPENDIX E

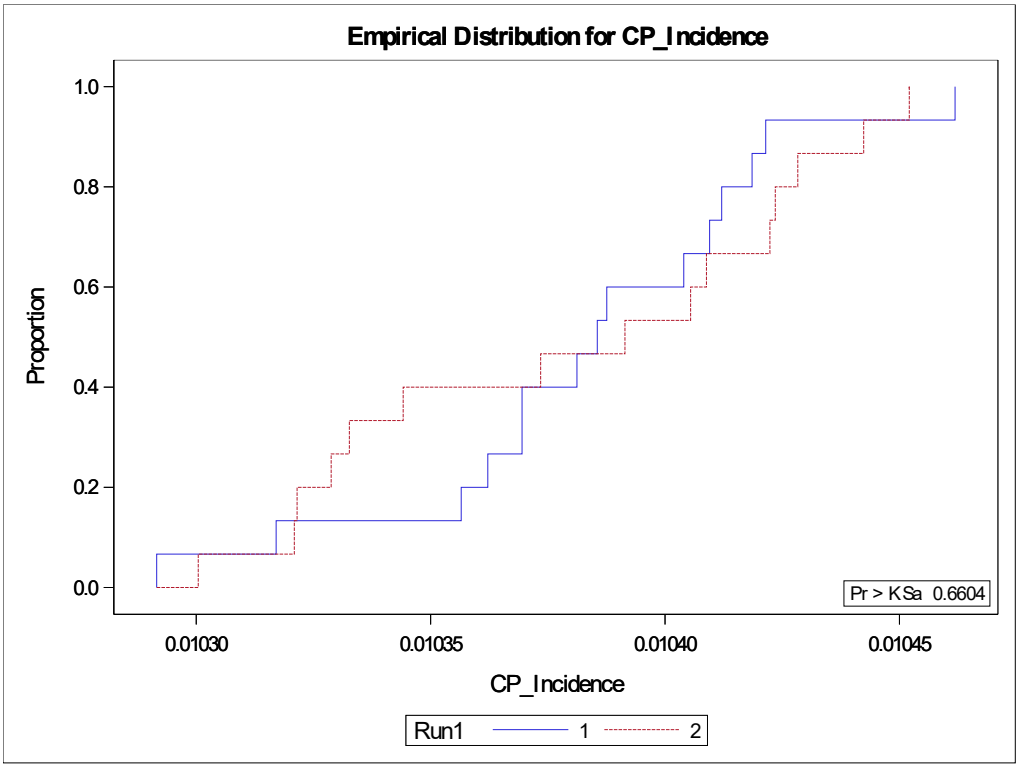
STATISTICAL TEST RESULTS TO DETERMINE THE ADEQUATE NUMBER OF RUNS FOR EACH EXPERIMENT

Table E.1. Chickenpox incidence comparing two sets of 15 runs



Wilcoxon Scores (Rank Sums) for Variable CP_Incidence Classified by Variable Run1					
Run1	**N**	**Sum of Scores**	**Expected Under H0**	**Std Dev Under H0**	**Mean Score**
1	15	229.0	232.50	24.106445	15.266667
2	15	236.0	232.50	24.106445	15.733333
Average scores were used for ties.					

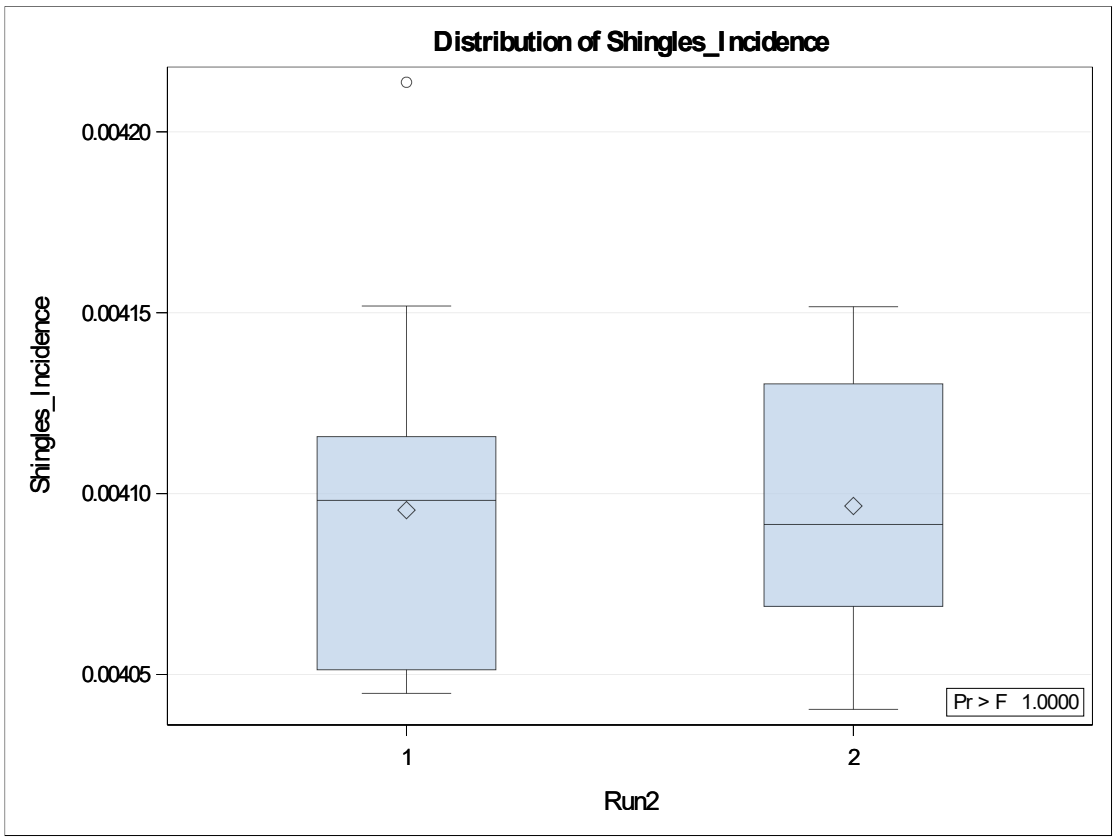
Wilcoxon Two-Sample Test	
Statistic	229.0000
Normal Approximation	
Z	-0.1244
One-Sided Pr < Z	0.4505
Two-Sided Pr > |Z|	0.9010
t Approximation	
One-Sided Pr < Z	0.4509
Two-Sided Pr > |Z|	0.9018
Z includes a continuity correction of 0.5.	



Kolmogorov-Smirnov Test for Variable CP_Incidence Classified by Variable Run1			
Run1	**N**	**EDF at Maximum**	**Deviation from Mean at Maximum**
1	15	0.133333	-0.516398
2	15	0.400000	0.516398
Total	30	0.266667	
Maximum Deviation Occurred at Observation 23			
Value of CP_Incidence at Maximum = 0.010344			

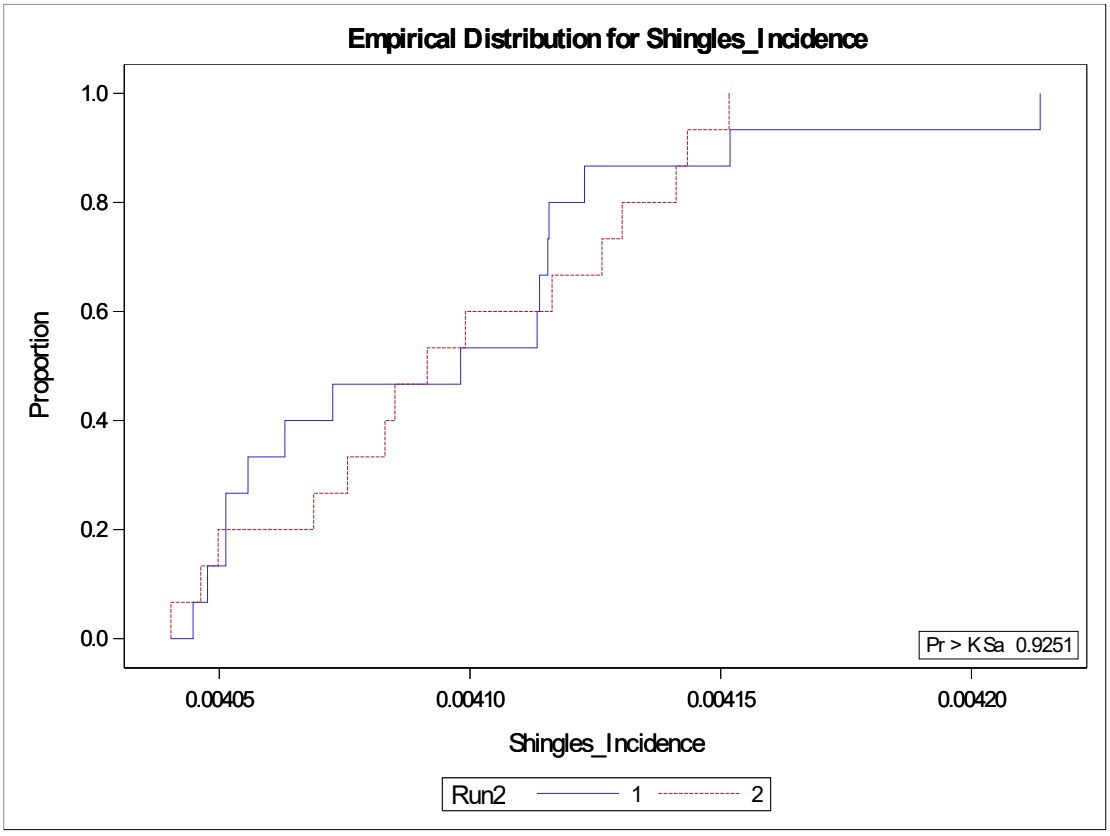
Kolmogorov-Smirnov Two-Sample Test (Asymptotic)			
KS	0.133333	**D**	0.266667
KSa	0.730297	**Pr > KSa**	0.6604

Table E.2. Shingles incidence comparing two sets of 15 runs



Wilcoxon Scores (Rank Sums) for Variable Shingles_Incidence Classified by Variable Run2					
Run2	**N**	**Sum of Scores**	**Expected Under H0**	**Std Dev Under H0**	**Mean Score**
1	15	223.0	232.50	24.106445	14.866667
2	15	242.0	232.50	24.106445	16.133333
Average scores were used for ties.					

Wilcoxon Two-Sample Test	
Statistic	223.0000
Normal Approximation	
Z	-0.3733
One-Sided Pr < Z	0.3544
Two-Sided Pr > |Z|	0.7089
t Approximation	
One-Sided Pr < Z	0.3558
Two-Sided Pr > |Z|	0.7116
Z includes a continuity correction of 0.5.	



Kolmogorov-Smirnov Test for Variable Shingles_Incidence Classified by Variable Run2			
Run2	**N**	**EDF at Maximum**	**Deviation from Mean at Maximum**
1	15	0.40	0.387298
2	15	0.20	-0.387298
Total	30	0.30	
Maximum Deviation Occurred at Observation 11			
Value of Shingles_Incidence at Maximum = 0.004063			

Kolmogorov-Smirnov Two-Sample Test (Asymptotic)			
KS	0.100000	**D**	0.200000
KSa	0.547723	**Pr > KSa**	0.9251

APPENDIX F

FULL LIST OF PARAMETER VALUES FOR CHAPTER 5

Parameter	**Values**
Total Population	500,000
Population Density- Urban	0.03
Population Density- Rural	0.02
1st dose chickenpox vaccination	On at 100 years
2nd dose chickenpox vaccination	On at 100 years
Shingles Vaccination	Off
ProbabilityOf1stDoseVaccination	0.97,0.75,0.03
ProbabilityOf2ndDoseVaccination	0.979,0.821,0.333
ProbabitlityOf1stDoseEffective	1-uniform (0.16,0.24)
ProbabilityOf2ndDoseEffective	1-uniform (0.05,0.16)
ProbabilityCatchupGivenVacc	0
Weight_vacc_acceptor	65
Weight_vacc_hesitator	30
Weight_vacc_rejector	5
WaningOfImmunityRateCPVacc	Uniform (0.01,0.03)
WaningOfImmunityRateCPVacc2ndDose	0
riskPossibilityShinglesfromCPVacc	0.05
probFebrileSeizure	0.0006
Shingles Vaccination	Off
ageToCheck1stDoseCoverage	2 years
ageToCheck2ndDoseCoverage	7 years
Exogenous Infection Rate	17.83
Pref. Mixing Age	1-9
Duration of exogenous boosting	5
Shingles connection range modifier	0.124
Shingles waning coefficient	0.63
Probability of shingles reactivation	0.05
Initialization	EQ_NoVacc
Enable bimodal shingles immunizing timer	Checked
Min_ageForDosAccel	0
Max_ageForDosAccel	19
ProbabilityOrDosAcc	0.05
DurationCP	Uniform (5,9)
durationCPweak	Uniform (4,8)
probCPDisease on Contact	0.781
probCPDiseaseOnContactWithShingle	0.2343
probCPDiseaseOnContactWithBreakthrough	0.2343
probFullDiseaseOnBreakthroughInfection	0.05
timeToRecoveryCP	Uniform (0,4) *day
probabilityOfComplicationDeathCP	0.000128

timeToNotInfectiousShingles	Uniform (7,20) * day
timeToRecoveryShingles	Triangular (7,14,70)
waningOfImmunityCoefficientShingles	0.63
DurationOfExogenousBoosting	5 years
WaningOfImmunityRateShingles	0.04*waningOfImmunityCoefficientShingles
shinglesRecurrenceRate	Uniform (0.0022,0.0076)
connectionRange_Pref	21.245
connectionRange_Norm	8.958
baseContactRate_Pref	20
baseContactRate_Norm	3
burnPeriod	75 years
discountingBegins	100 years (whenever we start vaccination)
Total Model Run	175 years

Sensitivity 1: Vaccine attitude 1 (high coverage)

Parameter	Values
Weight_vacc_acceptor	80
Weight_vacc_hesitator	15
Weight_vacc_rejector	5

Sensitivity 2: Vaccine attitude 2 (low coverage)

Parameter	Values
Weight_vacc_acceptor	65
Weight_vacc_hesitator	15
Weight_vacc_rejector	20

Sensitivity 3: Vaccine waning of immunity rate 1

Parameter	Values
waningOfImmunityRateCPVacc	0.0
waningOfImmunityRateCP2ndDose	0.0

Sensitivity 4: Vaccine waning of immunity rate 2

Parameter	Values
waningOfImmunityRateCPVacc	0.05
WaningOfImmunityRateCPVacc2ndDose	0.02

Sensitivity 5: Primary vaccine failure 1

Parameter	Values
ProbabitlityOf1stDoseEffective	1-0.09
ProbabilityOf2ndDoseEffective	1-0.05

Sensitivity 6: Primary vaccine failure 2

Parameter	Values
ProbabitlityOf1stDoseEffective	1-0.24
ProbabilityOf2ndDoseEffective	1-0.16

APPENDIX G

FULL LIST OF PARAMETER VALUES FOR CHAPTER 6

General parameter sets:

Parameter	**Values**
Total Population	500,000
Population Density- Urban	0.03
Population Density- Rural	0.02
1st dose chickenpox vaccination	On at 100 years
2nd dose chickenpox vaccination	On at 100 years
Shingles Vaccination	Off
ProbabilityOf1stDoseVaccination	0.97,0.75,0.03
ProbabilityOf2ndDoseVaccination	0.979,0.821,0.333
ProbabitlityOf1stDoseEffective	1-uniform (0.16,0.24)
ProbabilityOf2ndDoseEffective	1-uniform (0.05,0.16)
ProbabilityCatchupGivenVacc	0
Weight_vacc_acceptor	65
Weight_vacc_hesitator	30
Weight_vacc_rejector	5
WaningOfImmunityRateCPVacc	Uniform (0.01,0.03)
WaningOfImmunityRateCPVacc2ndDose	0
riskPossibilityShinglesfromCPVacc	0.05
probFebrileSeizure	0.0006
Shingles Vaccination	Off
ageToCheck1stDoseCoverage	2 years
ageToCheck2ndDoseCoverage	7 years
Exogenous Infection Rate	17.83
Pref. Mixing Age	1-9
Duration of exogenous boosting	5
Shingles connection range modifier	0.124
Shingles waning coefficient	0.63
Probability of shingles reactivation	0.05
Initialization	EQ_NoVacc
Enable bimodal shingles immunizing timer	Checked
Min_ageForDosAccel	0
Max_ageForDosAccel	19
ProbabilityOrDosAcc	0.05
DurationCP	Uniform (5,9)
durationCPweak	Uniform (4,8)
probCPDisease on Contact	0.781
probCPDiseaseOnContactWithShingle	0.2343
probCPDiseaseOnContactWithBreakthrough	0.2343
probFullDiseaseOnBreakthroughInfection	0.05

timeToRecoveryCP	Uniform(0,4) *day
probabilityOfComplicationDeathCP	0.000128
timeToNotInfectiousShingles	Uniform (7,20) * day
timeToRecoveryShingles	Triangular (7,14,70)
waningOfImmunityCoefficientShingles	0.63
DurationOfExogenousBoosting	5 years
WaningOfImmunityRateShingles	0.04*waningOfImmunityCoefficientShingles
shinglesRecurrenceRate	Uniform (0.0022,0.0076)
connectionRange_Pref	21.245
connectionRange_Norm	8.958
baseContactRate_Pref	20
baseContactRate_Norm	3
burnPeriod	75 years
discountingBegins	100 years (whenever we start vaccination)
Total Model Run	175 years

Cost Effectiveness Parameters Sets:

Parameter	**Values**
qualityOfLifeBaseUnder50	0.855
qualityOfLifeCPUnder15	0.76
qualityOfLifeCPOver15	0.67
qualityOfLifeWeakUnder50	0.83
qualityOfLifeWeakOver50	0.76
qualityOfLifeShingles	0.59
qualityOfLifePHN	0.67
qualityOfLifeHospitalizedCP	0.36
qualityOfLifeHospitalizedShingle	0.32
probGPVisitCP	0.4
probGPVisitCPWeak	0.4
probGPVisitShingles	1.0
probEDVisitCP	0.035
probEDVisitShingle	0
tableFunctionChanceOfPHNByAge	0-48: 5% 49-60: 14.6% 61-70: 20.5% 70+: 33.8%
CustomDistributionPHNDuration	90-120 days: 25% 120-356 days: 50% 356-700 days: 25%
probabilityOfComplicationDeathShingle	0.000154
costProductivityLossCP	280.84
costProductivityLossHospitalized	224.1
costProductivityLossShinglesUnder50	666.44

costProductivityLossHospitalizedShinglesUnder50	147.01
costProductivityLossPHNUnder50	1720.99
costProductivityLossShinglesOver50	345.41
costProductivityLossHospitalizedShinglesOver50	76.19
costProductivityLossPHNOver50	891.98
costPersonalExpenseCPUnder4	105.60
costPersonalExpenseCPOver4	43.84
costPersonalExpenseShingle	84.86
costGPVisitCP	40.96
costEDVisitCP	139
costGPVisitShingle	84.95
costEDVisitShingle	139
costPerPrescriptionMedCP	0.75
costPerPrescriptionMedShingle	58.31
CostShingleVacc	0
CostCPVaccDose1	55.22
CostCPVaccDose2	55.22
costPerDayHospitalizedCP	1523
costPerDayHospitalizedShingle	929.81
tfFracHospitalizedCPbyAge	0-1 = 1.8% 2-4 = 0.4% 5-11 = 0.2% 12-18= 0.4% 19-24 = 0.5% 25-44 = 1.4% 45-64 = 1.9% 65+ = 7%
tfLOSHospitalizedbyAge	<1 = 2.92 1-4 = 3.23 5-9 = 4.30 10-14 = 5.13 15-19 = 8.86 20+ = 5.70
tfFracHospitalizedShinglebyAge	0-4: 0.0055 5-14: 0 .0035 15-44: 0.0028 45-64: 0.007 65+: 0.0265
tfLOSHospitalizedShinglebyAge	0-4: 5.1 days 5-14: 4.6 days 15-44: 8 days 45-64: 11.6 days 65+: 20 days
costFebrileSeizures	139
DiscountRateQALY	1.5

DiscountRateCosts	1.5

Sensitivity 1: Vaccine attitude 1 (high coverage)

Parameter	Values
Weight_vacc_acceptor	80
Weight_vacc_hesitator	15
Weight_vacc_rejector	5

Sensitivity 2: Vaccine attitude 2 (low coverage)

Parameter	Values
Weight_vacc_acceptor	65
Weight_vacc_hesitator	15
Weight_vacc_rejector	20

Sensitivity 3: Low vaccine waning of immunity rate

Parameter	Values
waningOfImmunityRateCPVacc	0.0

Sensitivity 4: Low vaccine waning of immunity rate

Parameter	Values
waningOfImmunityRateCPVacc	0.05
WaningOfImmunityRateCPVacc2ndDose	0.02

Sensitivity 5: Primary vaccine failure low

Parameter	Values
ProbabitlityOf1stDoseEffective	1-0.09
ProbabilityOf2ndDoseEffective	1-0.05

Sensitivity 6: Primary vaccine failure high

Parameter	Values
ProbabitlityOf1stDoseEffective	1-0.24
ProbabilityOf2ndDoseEffective	1-0.16

Sensitivity 7: No discounting the benefits

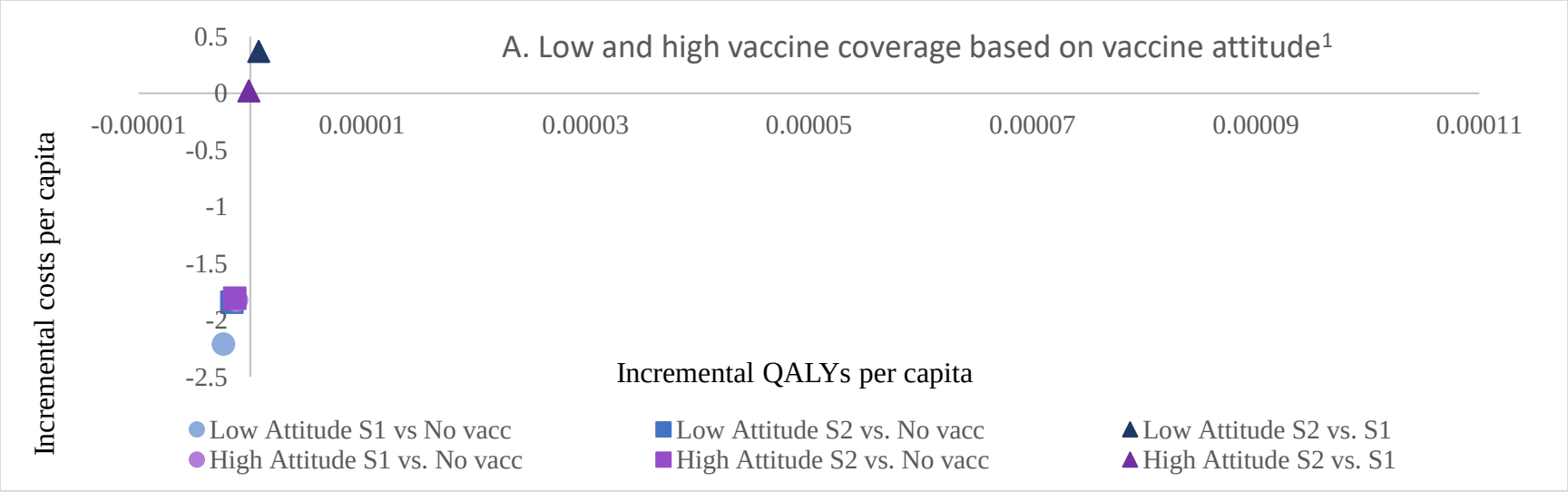
Parameter	Values
ProbabitlityOf1stDoseEffective	1-0.09

Sensitivity 8: Shorter duration of boosting

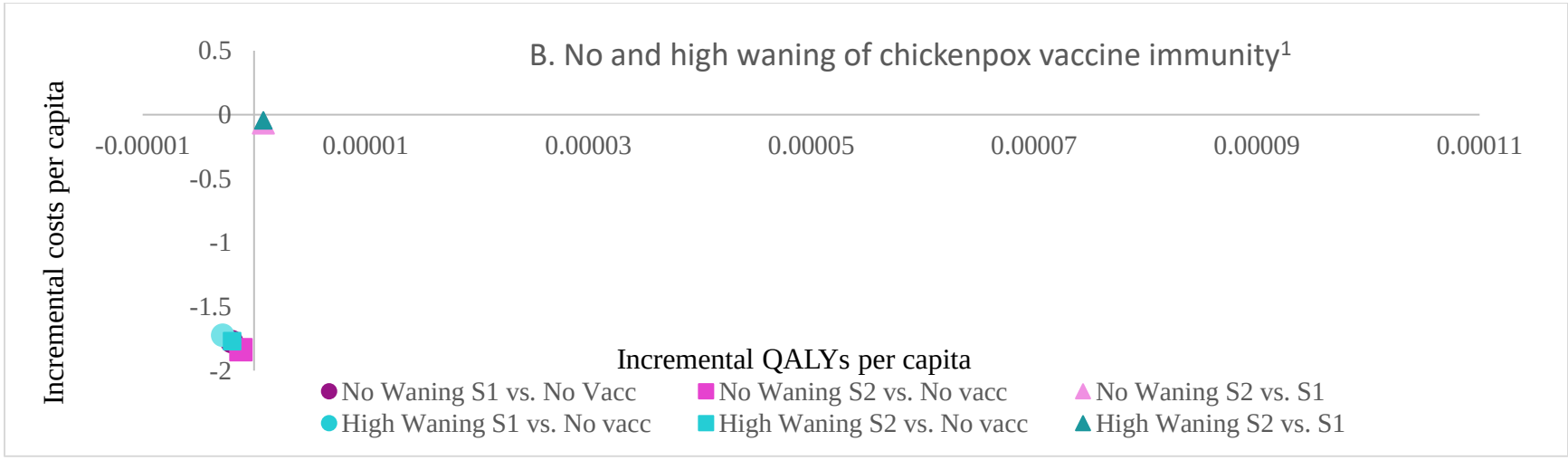
Parameter	Values
Duration of Exogenous Boosting	2 years
Shingles waning coefficient	0.5

APPENDIX H

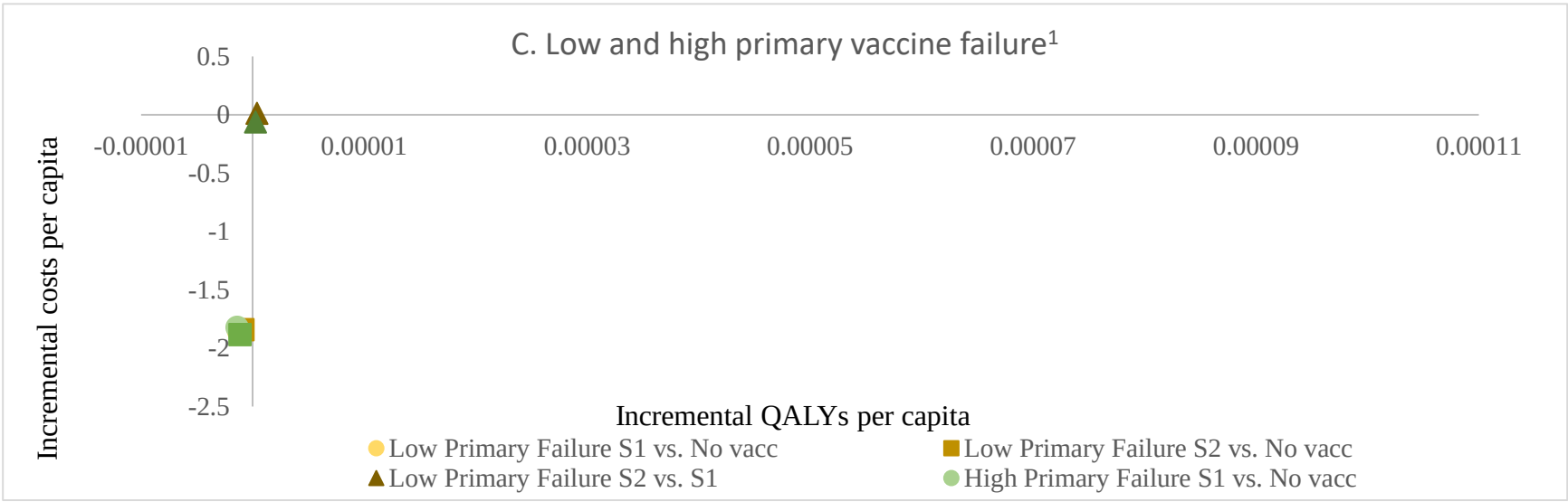
FIGURES FROM SCENARIO ANALYSES CHAPTER 6



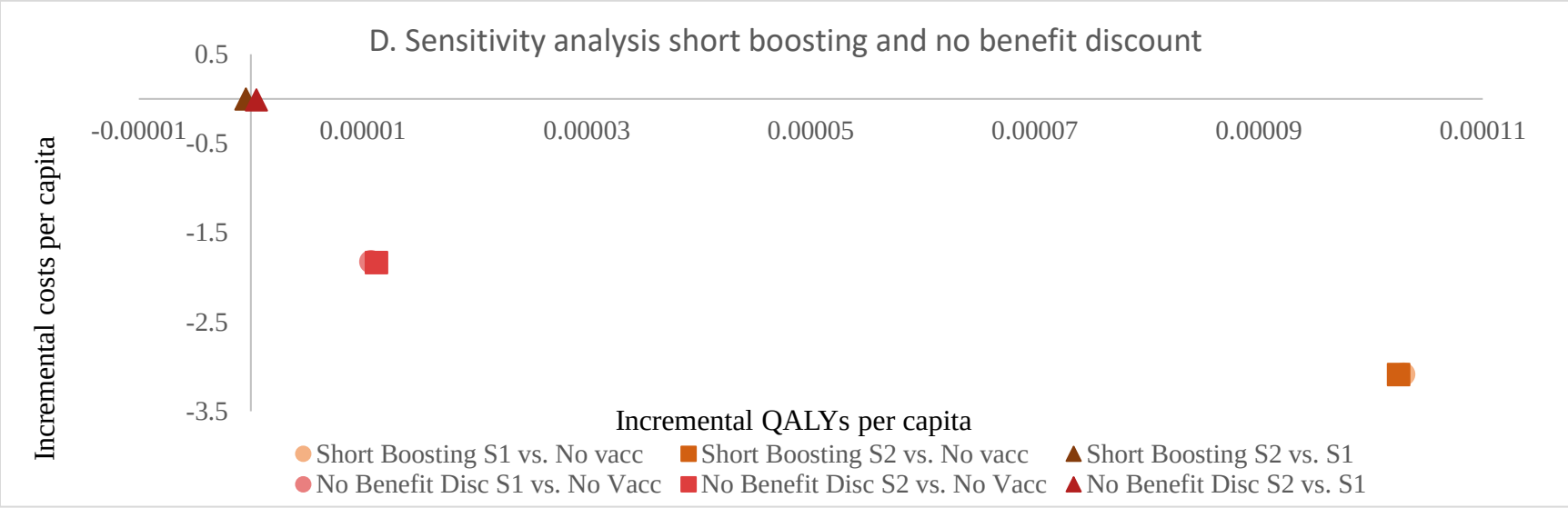
[1]Low attitude= shifting 15% of vaccine hesitant individuals to rejectors (low coverage); High attitude= shifting 15% of vaccine hesitant individuals to acceptors high coverage)



[1]No waning= 0% waning of chickenpox vaccine immunity; high waning= 5% waning of chickenpox vaccine immunity

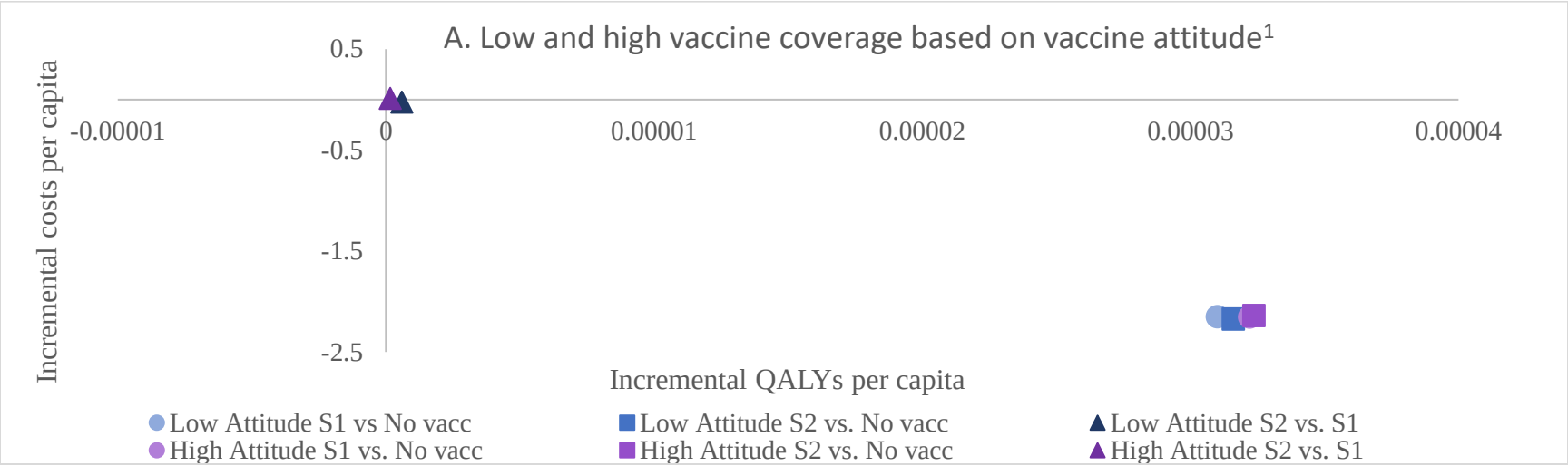


[1]Low primary vaccine failure 1st dose= 9 and 2nd dose= 5%; high primary vaccine failure 1st dose= 24% and 2nd dose= 16%.

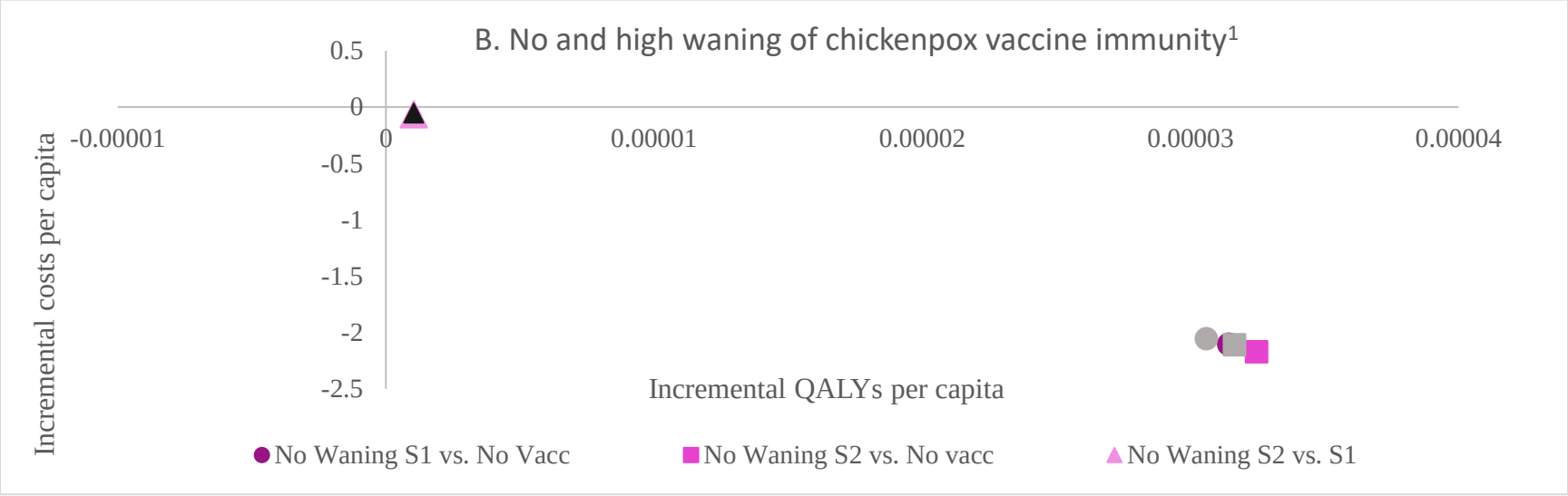


[1]Duration of boosting = 2 years and waning of immunity rate = 0.45; [2]No discounting of quality adjusted life years; therefore one QALY in the present is equal to one QALY in the future.

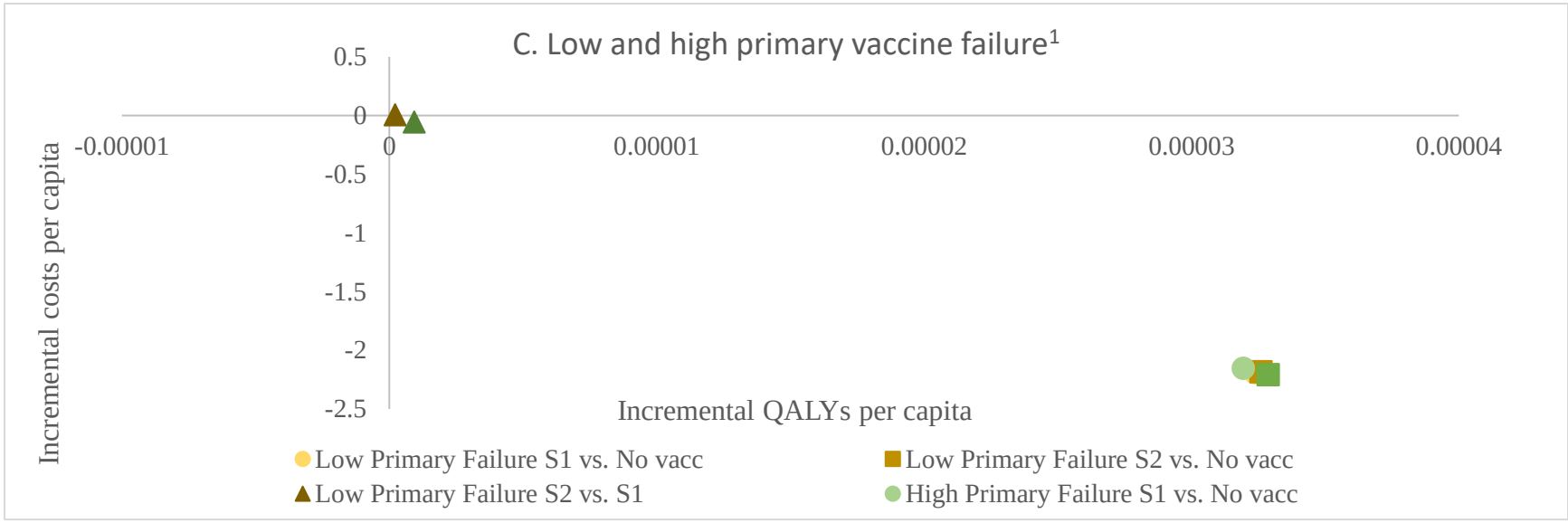
Figure H.1. Scenario analysis cost-effectiveness plane -Median incremental costs and QALYs per capita by scenario *with* shingles (societal perspective)



[1]Low attitude shifting 15% of vaccine hesitant individuals to rejectors (low coverage); High attitude shifting 15% of vaccine hesitant individuals to acceptors (high coverage)



[1]No waning= 0% waning of chickenpox vaccine immunity; high waning= 5% waning of chickenpox vaccine immunity

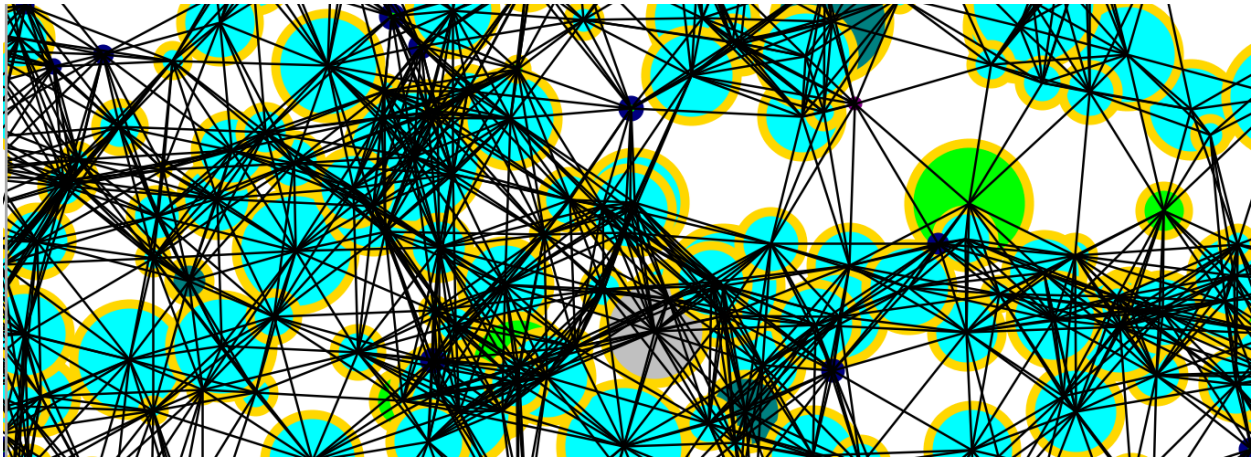


[1]Low primary vaccine failure 1st dose= 9 and 2nd dose= 5%; high primary vaccine failure 1st dose= 24% and 2nd dose= 16%.

Figure H-2. Scenario analysis cost-effectiveness plane -Median incremental costs and QALYs per capita by scenario *without* shingles (societal perspective)

APPENDIX I

NETWORK DIAGRAM



Centre Colour
Green= Susceptible
Light Blue= Recovered
Red= Infected

Outside Colour
Blue= Protected through 1st dose vaccination
Dark Green= Protected through 2nd dose vaccination
Yellow= Not protected

*Black lines between agents signify connections